

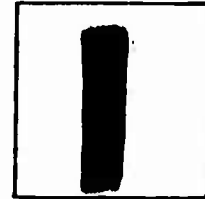
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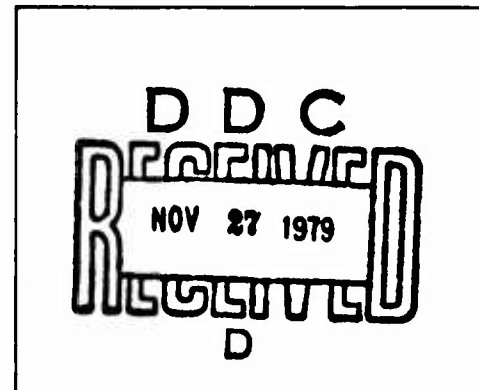
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Washington, D.C. 20012

This report covers the period (1 October 1977 thru 30 September 1978).

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TABLE OF CONTENTS

	<u>Page</u>
Unit Summary Sheet	1
Table of Publications and Presentations, FY-78	5
Work Unit Numbers and Protocol Titles by Departments	
<u>DEPARTMENT OF MEDICINE</u>	
<u>General Medicine</u>	
1004 Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine (FY-77 O).	17
<u>Nephrology and Renal Dialysis Service</u>	
1112 Use of Minoxidil in the Treatment of Severe, Uncontrolled or Poorly Controlled Hypertension (FY-75 O)	19
1120 Bone Marrow Reserve and WBC Survival in Patients with Chronic Renal Failure (FY-76 T).	20
1121 Combined Prednisone and Cytoxan Therapy Coupled with Plasma Exchange in the Treatment of Antiglomerular Basement Membrane Mediated Renal Disease (FY-76 O).	21
1122 Evaluation of Urinary Creatinine as a Reference Point for Comparing Body Potassium Determinations (FY-77 O).	22
1123 Effect of Acidosis, Nutritional Status and Aldosterone on Potassium Metabolism in Patients with Stable Chronic Renal Failure (FY-77 T).	23
1124 The Effect of Hyperuricemia on Chronic Renal Failure (FY-78 O).	24

DEPARTMENT OF MEDICINE (continued)

Page

Cardiology Service

- | | | |
|------|--|----|
| 1212 | Computer Assisted System for Coronary Artery Disease Evaluation (FY-78 O). | 25 |
| 1213 | Electron Microscopic Evaluation of Cardiovascular Guidewires (FY-73 O). | 27 |

Endocrinology-Metabolic Service

- | | | |
|------|--|----|
| 1308 | Inderal Kinetics in Hyperthyroidism (FY-74 O). | 28 |
| 1310 | TRH in Patients with Hypothalamic-Pituitary Thyroid Disease (FY-72 O). | 29 |
| 1311 | Treatment of Thyroid Storm with Anion-Exchange Resin (FY-74 O). | 30 |
| 1314 | Stimulation and Suppression of Plasma Prolactin in Patients with Pituitary Disease (FY-73 T). | 31 |
| 1320 | Effect of Lilly Compound 83636 on Plasma Prolactin in Humans with Galactorrhea, Probable Pituitary Tumors or Breast Cancer (FY-75 T) | 33 |
| 1321 | Effects of Cancer Chemotherapy Agents on Endocrine Function (FY-74 T) | 34 |
| 1329 | Lithium Effects on Thyroid (FY-73 O). | 35 |
| 1331 | Effect of Iodine and Lithium on the Release of Thyroxine from the Thyroid Gland on Patients with Thyrotoxicosis (FY-75 PO) | 36 |
| 1332 | Differentiation of Malignant from Benign Thyroid Nodules: Assessment of New Diagnostic Techniques (FY-75 O). | 37 |
| 1334 | The Regulation of Extrathyroidal Conversion of Thyroxine (T4) to Triiodothyronine (T3) (FY-75 O). | 38 |
| 1336 | Constant Infusion of TRH in Acromegaly (FY-75 T) | 39 |
| 1337 | Growth Hormone Response to TRH in Acromegaly (FY-75 T). | 40 |
| 1338 | Hormonal and Metabolic Changes in Hypertension (FY-75 T). | 41 |

DEPARTMENT OF MEDICINE (continued)

Page

Endocrinology-Metabolic Service

1339	Effect of Lithium on Intrathyroidal Iodine Content (FY-76 T).	42
1340	Use of Fluorescent Thyroid Scanning to Evaluate Iodine Content (FY-76 O).	43
1342	Dietary Influence on Prolactin Secretion (FY-76 T).	45
1345	Conversion of Testosterone to Estradiol (FY-76 O).	46
1346	Thyroid Function Tests in Cord Blood, Maternal Sera and Amniotic Fluid (FY-76 PO).	47
1347	Investigations into the Physiology of L-Reverse T-3 (rT3) and -3-'Diiodothyronine (3-3'T2) (FY-76 O).	48
1348	Correlation of Dose and Duration of Exogenous Steroid Therapy with Recovery of Hypothalamic -Pituitary - Adrenal Function (FY-76 C).	49
1349	Evaluation of the Use of a Specific Radioimmunoassay for Compound S in the Interpretation of the Results of Metyrapone Testing (FY-76 C).	50
1351	Effects of Cyproheptadine on Pituitary Secretion (FY-77 T).	51
1352	Echocardiographic Findings in Acromegaly (FY-77 PC).	52
1353	The Regulation of T4 Conversion. A Grant Proposal (FY-77 O).	54
1354	Purification of Testosterone-estradiol Binding Globulin (FY-77 O).	55
1355	The Effect of Short-Term High-Dose Steroid upon Thyroidal Release in Thyrotoxicosis (FY-77 O).	56
1356	The Pituitary-Gonadal Axis and Testicular Function in Hyperthyroidism (FY-77 PO).	57
1357	Effect of T3 and rT3 on Extracellular Cyclic Nucleotide Levels in Humans (FY-77 O).	59
1358	The Effect of Obesity and Fasting on T3 Receptors in Circulating Mononuclear Cells (FY-77 O).	61

DEPARTMENT OF MEDICINE (continued)

Page

Endocrinology-Metabolic Service

1359	The Effect of Reverse T3 and 3,3'T2 on Thyroid Gland Secretion, T4 Degradation, and Iodide Leak in Thyrotoxic Patients (FY-77 O).	62
1360	Investigations Concerning T3 Production Rates (FY-77 O).	63
1361	Postoperative Changes in Free Testosterone and Sex-Hormone-Binding-Globulin (FY-77 O).	64
1362	Medical Treatment of Amenorrhea-Galactorrhea Syndrome with Vitamin B ₆ (Pyridoxine) (FY-77 O).	65
1363	Effect of T3 and rT3 on Plasma Cyclic Nucleotide Levels in Sheep (FY-77 PO).	66
1364	Effect of L-Tryptophan on LH and FSH Dynamics in Women (FY-77 O).	68
1365	Insulin Resistance in Diabetes: Relative Effect of Glucose and Amino Acids (FY-77 O).	69
1366	The Effect of Glucagon on Thyroidal Economy (FY-77 O).	70
1367	Effect of Methyldopa on Serum LH and Testosterone in Hypertensive Men (FY-77 O).	71
1368	Effect of Dietary Phosphate on Serum Levels of Vitamin D Metabolites in Hypoparathyroidism (FY-77 O).	72
1369	A Prospective Study of the Effects of Propranolol on Hypercalcemia in Hyperthyroidism and Hyperparathyroidism (FY-77 O).	74
1370	Sex Steroid Receptors in the Human Thyroid Gland (FY-77 O).	75
1371	Glucose Regulation of Peripheral Thyroidal Economy in Fasted Subjects (FY-77 PO).	76
1372	Alteration in the Thyrotropin (TSH) Response to Thyrotropin-Releasing Hormone (TRH) Stimulation in Obesity and Fasting (FY-77 O).	77
1373	The Effect of Protein Ingestion on Thyroid Hormone Economy (FY-77 PO).	78

DEPARTMENT OF MEDICINE (continued)

Page

Endocrinology-Metabolic Service

1374	Evaluation of Testosterone Reserve in Infertile Men. (FY-77 O).	79
1375	Effect of Separating Protein from Carbohydrate in the Dietary Treatment of Diabetes (FY-77 T).	80
1376	Effect of Amitriptyline and Amantadine on Growth Hormone Dynamics in Acromegaly (FY-77 O).	81
1377	Effect of Dietary Tryptophan Content on Food Intake in Obese Subjects (FY-77 T).	82
1378	Effect of 4-Hour ACTH Infusion on Plasma Steroids (FY-77 T).	83
1379	Effect of Post-Weaning Undernutrition on Reproductive Hormones in Rats (FY-77 O).	84
1380	Effect of Thyroid Status on the Hormonally-Induced Cyclic AMP Responses of the Kidney (FY-77 PO).	85
1381	Estradiol (E ₂) Receptors in Rat Thyroid Glands (FY-77 O).	87
1382	Measurement of Steroids in Fluid Obtained by Micropuncture from Rat Seminiferous Tubules and Epididymis (FY-77 O).	88
1383	Measurement of Hemoglobin A-1-C in the Assessment of the Efficacy of Diabetic Treatment (FY-77 O).	89
1384	The Effect of Isoniazide (INH) on Prolactin, Gonadal Function and Pyridoxine Vitamin B ₆ Metabolism (FY-77 O).	90
1385	Serial Changes in Free Testosterone during Pregnancy: Correlation with HCG Levels and Fetal Sex (FY-78 O).	91
1386	The Effect of Δ -Testolactone (Teslac) in Male Infertility (FY-78 O).	92
1387	Acute Responses to Estrogen in Men with Prostate Carcinoma (FY-78 O).	93
1388	The Development of a Radioimmunoassay for Thyronine and 3,5-T ₂ . (FY-78 O).	94

<u>DEPARTMENT OF MEDICINE</u>		<u>Page</u>
<u>Endocrinology-Metabolic Service</u>		
1389	The Effect of Dietary Carbohydrates on T3 Receptor Kinetics (FY-78 O).	95
1390	Investigations Concerning the Physiology of Iodothyronines during Fasting (FY-78 O).	96
1391	Regulation of the Initiation of Thyroid Hormone Action (FY-78 O).	97
1392	Steroid Transfer across the Blood-Cerebrospinal Fluid Barrier in the Rhesus Monkey (FY-78 PO).	98
1393	T3 Receptors in Normal and Fasting Rats (FY-78 PO).	99
1394	The Development of a Radioimmunoassay of Triiodothyronine (FY-78 O).	100
1395	T ₄ to T ₃ Conversion: Effect of Modulation of Glucose Metabolism (FY-78 O).	101
1396	T ₄ to T ₃ Conversion: Effect of Somatostatin Administration (FY-78 O)	102
1397	The Effect of Free Fatty Acids on Serum Reverse T3 and T3 Levels (FY-78 O).	103
1398	Studies on the Pathogenesis of Hypocalcemia in Tumors Associated with Osteoblastic Metastases (FY-78 O).	104
1399	An Assessment of Parathyroid Hormone (PTH) Levels in Normal Subjects and in Patients with Disorders of Calcium Metabolism (FY-78 O).	106
1300-78	The Development of a Radioimmunoassay for 3-Monoiodothyronine (3-T1) (FY-78 PO).	107
1301-78	The Effect of Δ -Testolactone (Teslac) on 5 α -Reductase in Rats (FY-78 O).	108
1302-78	Effect of Obesity and Fasting on Divalent Ion, PTH, and Calcitonin Dynamics (FY-78 O).	109
1303-78	Studies on the Alterations in Drug Metabolism in Hyperthyroidism (FY-78 O).	110
1304-78	Radionuclide Assessment of Cardiac Function in Patients with Acromegaly (FY-78 O).	111

<u>DEPARTMENT OF MEDICINE (continued)</u>		<u>Page</u>
<u>Endocrinology-Metabolism Service</u>		
1305-78	Breast Carcinoma and Thyroid Hormone Receptors (FY-78 O).	113
<u>Gastroenterology Service</u>		
1408	Bile Salt Clearance in Chronic Active Hepatitis (FY-76 PO).	114
1410	Percutaneous (Blind) Versus Laparoscopic (Direct Vision) Liver Biopsy in Assessing Chronic Active Hepatitis (FY-76 O).	115
1415	Esophageal Clearing: Quantitated by Radioisotope Scan (FY-77 PO).	116
1416	Esophageal Emptying in Achalasia: Quantitated by a Radioisotope Method (FY-77 PO).	117
1417	Plasma Ligandin in Liver Disease (FY-77 O).	118
1418	Preliminary Clinical Evaluation of Triamcinolone Acetate Acetonide Retention Enemas in the Treatment of Distal Ulcerative Colitis (FY-77 C).	119
1419	Cricopharyngeal Bar: A Video Manometric Study (FY-77 O).	120
1420	Adenyl Cyclase and Guanyl Cyclase in the Cat Esophagus (FY-78 PO).	121
1421	Immune Characteristics of Peripheral Blood Lymphocytes in Patients on Cimetidine (FY-78 O).	123
1422	The Sequential Staging of the Liver in Hodgkin's Disease with Laparoscopy and Laparotomy (FY-78 O).	124
1423	A Study of Trifluoroisobutyl Cyanoacrylate Polymer in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum (FY-78 O).	125
1424	A Double Blind Study of Long Term Maintenance Cimetidine Therapy on Gastroesophageal Reflux Diseases (FY-78 O).	127

<u>DEPARTMENT OF MEDICINE (continued)</u>		<u>Page</u>
<u>Gastroenterology Service</u>		
1425	Pulmonary Aspiration from Gastroesophageal Reflux Defined by Pulmonary Scintiscan and Overnight Intra-Esophageal pH Monitoring (FY-78 O).	128
1426	The Effect of Indomethacin on Experimentally Induced Acid Stricture on the Cat Esophagus (FY-78 O).	130
<u>Hematology-Oncology Service (CALGB)</u>		
1516	CALGB #7291, Role of Postoperative Radiotherapy, and Combinations of Dactinomycin, Vincristine, Cyclophosphamide and Adriamycin in Childhood Rhabdomyosarcoma by Acute Leukemia Group B, Southwestern Cancer Chemotherapy Study Group and Childrens' Cancer Study Group A (FY-73 O).	133
1517	CALGB #7331, Hydroxyurea 6-Mercaptopurine and Prednisone with or without Vincristine and Daunorubicin in the Treatment of the Resistant Phase of Chronic Granulocytic Leukemia (FY-74 C).	137
1518	CALGB #7383, Clinical Trial of VP 16-213 (4'-dimethyl-epipodophyllotoxin-B-D-ethylidene-glucoside) in Advanced Neoplastic Disease (FY-74 T).	139
1519	CALGB #7361, Multiple Myeloma Resistant to L-Phenylalanine Mustard Treated with Cyclophosphamide (Cytosan), Prednisone, 1,3,-bis-(2-Chloroethyl-1-Nitrosourea (BCNU) (FY-74 C).	140
1520	CALGB #7411, Combination Chemotherapy in Induction and for Standard Risk and Combination Chemotherapy Plus Cranial Irradiation Plus Daunorubicin for Increased Risk Followed by Maintenance with Continuous Versus Intermittent 6-MP Plus Methotrexate Reinforcement and Subsequent Immunotherapy. (Maintenance Treatment of Patients with ALL under the Age of 21 (FY-75 O).	142

DEPARTMENT OF MEDICINE (continued)

Page

Hematology-Oncology Service

1528	CALGB #7391, Clinical Trial of Radiotherapy and Chemotherapy (Cyclophosphamide) Vincristine and Actinomycin in Managing Non-Metastatic Ewing's Sarcoma (FY-75 O).	147
1532	CALGB #7451, Combination Radiotherapy and Chemotherapy of Stage III Hodgkin's Disease (Phase III) (FY-75 O).	149
1533	CALGB #7461, Primary Treatment of Multiple Myeloma: Comparison of L-PAM Plus Prednisone and BCNU Plus Prednisone and CCNU Plus Prednisone with or without Intermittent Vincristine and Prednisone (FY-75 O).	151
1534	CALGB #7521, A Comparative Study of the Value of Immunotherapy with MER as Adjuvant to Induction in Two Maintenance Chemotherapy Programs in Acute Myelocytic Leukemia (FY-76 O).	153
1535	CALGB #7581, Long Term Surgical Adjuvant Systemic Chemotherapy with or without Adjuvant Immunotherapy in Mammary Carcinoma: A Comparative Study of Cytoxan, Vincristine, Methotrexate, 5-Fluorouracil, Prednisone, Vs Cytoxan, Methotrexate and 5-Fluorouracil Vs Cytoxan, Methotrexate, 5-Fluorouracil and MER (FY-76 O).	156
1536	CALGB #7531, Treatment of Chronic Myelocytic Leukemia with the Aim of the Prevention of Myeloblastic Transformation. A Phase III Study. (FY-76 T).	161
1537	CALGB #7551, Combination Chemotherapy and Radiotherapy for Stage IV Hodgkin's Disease (FY-76 O).	162
1538	CALGB #7552, Combination Chemotherapy and Immunotherapy for Previously Treated Stage IIIB and IV Hodgkin's Disease (FY-76 O).	164
1539	CALGB #7541, Combination Chemotherapy and Immunotherapy in Previously Untreated Stage III and IV Neuroblastoma. A Phase III Study (FY-76 O).	167
1541	CALGB #7542, Treatment of Non-Hodgkin's Lymphomas in Children: Methotrexate, Vincristine, Dexamethasone, Cyclophosphamide, 6-Mercaptopurine Plus Radiation Therapy to Involved Areas. A Phase III Study (FY-76 C).	169
1542	CALGB #7583, Adjuvant Chemotherapy in Osteogenic Sarcoma, Adriamycin Vs Sequential Adriamycin, High Dose Methotrexate-Citrovorum Factor Vs Sequential Adriamycin- Cyclophosphamide (FY-76 O).	173

DEPARTMENT OF MEDICINE, (continued)

Page

Hematology-Oncology Service

1543	CALGB #7651, Combination Chemotherapy of Stage III and IV Lymphocytic Lymphoma (Lymphosarcoma) in Adults with or without Radiotherapy Consolidation (FY- 76 O).	175
1546	CALGB #7611, Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years with Vincristine, Prednisone, Methotrexate, L-Asparaginase, and 6-Mercaptopurine, Plus Cranial Irradiation (FY-77 O).	180
1547	CALGB #7682, Combination Chemotherapy or Chemoimmunotherapy for Metastatic Recurrent or Inoperable Carcinoma of the Breast (FY-77 O).	182
1548	CALGB #7681, Investigation of the Effects of Adriamycin with and without Added MER in Soft Tissue Sarcomas (FY-77 O).	184
1551	CALGB #7612, Therapy of Acute Lymphocytic Leukemia in Adults: A Comparison of Vincristine, Prednisone and L-Asparaginase (FY-77 O).	186
1552	CALGB #7632, Chemotherapy in Indolent Chronic Lymphocytic Leukemia (FY-77 O).	188
1553	CALGB #7661, Multiple Myeloma Resistant to Melphalan Treated with Cyclophosphamide, Adriamycin, BCNU, and Prednisone (FY-77 C).	189
1554	CALGB #7691, Comparison of Involved Field Radiotherapy with Involved Field Radiotherapy with Adjuvant MOPP Chemotherapy and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkin's Disease in Children (FY-77 O).	191
1555	CALGB Pilot Study #0702, Evaluation of Galactitol 1,2:5,6 -Dianhydro in the Treatment of Advanced Carcinoma of the Lung and Melanoma. A Phase III Study (FY-77 O).	194

DEPARTMENT OF MEDICINE (continued)

Hematology-Oncology Service

Page

1556	CALGB #7721, A Comparative Study of Adriamycin Vs Daunorubicin at Two Dose Levels for Induction and of 4-Week Cycle Vs 8-Week Cycle for Maintenance Chemotherapy in Acute Myelocytic Leukemia (FY-77 O).	196
1557	CALGB Pilot Study #0704, A Phase II Trial of Neocariznostatin in Carcinoma of the Bladder, Kidney, Pancreas, Stomach, Uterus, Ovary, Hepatoma, Acute Leukemia, or Malignant Melanoma (FY-77 O).	201
1558	CALGB #7761, A Study to Determine the Effectiveness of Single Vs Multiple Alkylating Agents with or without Adriamycin in the Primary Treatment of Multiple Myeloma (FY-78 O).	203
1559	CALGB #7781, Small Cell Carcinoma of the Lung: Localized Disease. A Phase III Study. Combination Chemotherapy Vs Alternating Chemotherapy Plus Radiotherapy with or without Immunotherapy (FY-78 O).	206
1601	WRAMC #7207, Use of Pentamidine Isothionate in Pneumonia Caused by or Suspected to be Caused by Pneumocystis Carciinii (FY-73 C).	215
1602	WRAMC #7301, The Use of Cholestyramine in Metastatic Carcinoma of the Prostate and Ovary and Other Malignancies (FY-73 C).	216
1603	WRAMC #7206, Use of Methyl-CCNU [1-(2-Chloroethyl)-3-(4-Methyl-1-Nitrosoethyl)-1-Nitrosourea] in the Treatment of Brain Tumor (FY-73 O).	217
1604	WRAMC #7205, Phase II, Combination Chemotherapy with Dimethyl Triazeno Imidazole Carboxamide and Adriamycin in Soft Tissue and Bone Sarcomas (FY-73 O).	219
1610	WRAMC #7307, Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast (FY-73 O).	220
1613	WRAMC #7402, Adjuvant Therapy of Stage II Testicular Carcinoma with Chemotherapy (Actinomycin-D and Chlorambucil), Radiation Therapy or Chemotherapy Plus Radiation Therapy after Retroperitoneal Lymph Node Dissection (FY-73 O).	221

DEPARTMENT OF MEDICINE (continued)PageHematology-Oncology Service (continued)

1621	WRGH #7208, Phase II Study, 5-Azacytidine in Acute Leukemia (FY-73 O).	222
1626	WRAMC #7405, Treatment of Advanced Renal Cell Carcinoma with a Combination of 1-(Chlorethyl)-3-Cyclohexyl-1-Nitrosourea (CCNU) and Bleomycin (FY-75 O).	223
1627	WRAMC #7404, Immunological Evaluation and Immunotherapy of Patients with Carcinoma of the Lung (FY-75 PO).	225
1628	WRAMC #7406, Chemoimmunotherapy of Carcinoma of the Large Bowel (FY-75 O).	228
1629	WRAMC #7407, Chemoimmunotherapy of Malignant Melanoma (FY-75 O).	231
1630	WRAMC #7408, Comparative Trial of Tamoxifen and Fluoxymesterone Plus Tamoxifen in Metastatic Breast Cancer (FY-75 O).	233
1634	WRAMC #7412, Metastatic Breast Carcinoma Study to Evaluate the Effect of Cyclophosphamide, Adriamycin and 5-Fluorouracil Vs Adriamycin, Dibromodulcitol and Vincristine Sequentially Alternating with Cyclophosphamide, Methotrexate and 5-Fluorouracil (FY-75 O).	234
1643	The Use of Auto-Factor IX Concentrate (Human) Dried in the Treatment of Patients with Bleeding Due to Factor VIII Inhibitors (FY-76 O).	237
1644	WRAMC #7501, Evaluation of Adriamycin and Cis-Platinum Combination Chemotherapy in Treatment of Malignant Disease. A Phase II Study (FY-75 O).	238
* 1647	Inhibition of Red Cell Pyridoxal Kinase by the Carbonyl Reagents, Isoniazid and Hydralazine. (FY-76 T).	557
1649	WRAMC #7602, Chemoimmunotherapy of Prostatic Carcinoma (FY-76 O).	239
1650	WRAMC #7603, Evaluation of Galactitol 1,2:5,6 Dihydro in the Treatment of Advanced Neoplastic Disease (FY-76 C).	240
1651	WRAMC #7604, Combination Chemotherapy for the Treatment of Advanced Gastric Carcinoma with Either 1-(Tetrahydro-2-Furyl)-5-Fluorouracil (Ftorafur), Adriamycin and Mitomycin-C Versus 5-Fluorouracil, Adriamycin and Mitomycin-C (FY-76 PO).	241

DEPARTMENT OF MEDICINE

		<u>Page</u>
<u>Hematology-Oncology Service</u>		
1652	WRAMC #7605, Combination Chemotherapy of Advanced Pancreatic Carcinoma with 5-Fluorouracil, Mitomycin-C and Streptozotocin (FY-76 O).	243
1653	WRAMC #7606, Phase I-II Study of High Dose Methotrexate (MTX) with Citrovorum Factor Rescue for Children and Adults with Metastatic Osteosarcoma and Advanced Gliomas of the Brain (FY-77 O).	244
1654	WRAMC #7601-A, The Treatment of Unresectable Bronchogenic Carcinoma with CCNU 2(2Chlorethyl)-3-Cyclohexyl-1-Nitrosourea, Cyclophosphamide, Adriamycin, Procarbazine, Hexamethylemalamine, Methotrexate and Irradiation (FY-77 O).	245
1655	WRAMC #7607, Chemoimmunotherapy of Carcinoma of the Lung Using High-Dose Methotrexate and Citrovorum Factor with or without BCG (FY-77 O).	247
1656	WRAMC #7608, The Use of Thymosin (F-5) in Patients with Carcinoma of the Esophagus. A Phase I Study. (FY-77 C).	248
1659	WRAMC #7703, Hepatic Artery Infusion with 5-Fluorouracil (FY-78 O).	249
1661	Polycythemia Vera Study Group Protocols 5,6,7, and 8. The Treatment of Thrombosis in Patients with Polycythemia Vera (FY-78 O).	251
1662	WRAMC #7704, Chlorozotocin in Metastatic Malignant Melanoma. Resistant to ICDT (FY-77 C).	261
1663	GOG #26, A Phase II Trial of Galactitol 1,2:5,6 Dianhydro in Patients with Advanced Pelvic Malignancies (FY-78 C).	262
<u>Pulmonary Disease Service</u>		
1701	Phagocyte Chemotaxis in Patients with Bronchogenic Carcinoma (FY-77 T).	263
1702	Effect of Unilateral Major Airway Obstruction on Maximal Expiratory Flow Volume Loop (FY-78 C).	264

DEPARTMENT OF MEDICINE (continued)

Dermatology Service

- | | | |
|------|--|-----|
| 1801 | Direct Immunofluorescence in Mixed Connective Tissue Disease. (FY-77 O). | 266 |
|------|--|-----|

Infectious Disease Service

- | | | |
|-------|--|-----|
| 1901 | The Efficacy of Antisera to Gram Negative Endotoxin in the Therapy of Gram Negative Sepsis (FY-75 O). | 267 |
| 1903 | Persistence of <u>T. Pallidum</u> in Neurosyphilis (FY-77 PO). | 269 |
| 1904 | Access Shunt Infections on Patients Undergoing Kidney Dialysis (FY 77 PO). | 270 |
| 1905 | Local Immune Responses to <u>Neisseria Gonorrhoeae</u> in Humans (FY-77 PO). | 271 |
| 1906 | The Limulus Lysate Assay for the Determination of Gram Negative Meningitis Septic Arthritis and Contamination of Intravenous Fluids (FY-78 O). | 274 |
| +1907 | Solid Phase Radioimmunoassay (SPIRA) for the Quantitation of IgG, IgM, and IgA Specific Antibody Levels in Sera from Patients with Straphylococcal and Streptococcal Infections (FY-78 T). | |
| 1908 | Evaluation of Sodium Stibogluconate (Pentostam ^R) in the Treatment of Cutaneous Leishmaniasis (FY-78 O). | 276 |
| 1909 | Immunological Evaluation of Patients with Leishmaniasis (FY-78 O). | 278 |

DEPARTMENT OF SURGERY

Peripheral Vascular Service

- | | | |
|------|---|-----|
| 2101 | Investigation of Vascular Injuries, Vascular Disease, Vascular Grafts and Operating Procedures (FY-69 PO). | 279 |
| 2103 | Heparin Dosage during Peripheral Vascular Reconstruction (FY-76 PC) | 281 |
| 2104 | Evaluation of the Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication (FY-77 O). | 282 |

DEPARTMENT OF SURGERY (continued)

Page

Peripheral Vascular Service

- 2105 Rapid Screening for Coagulation Abnormalities (FY-78 O). 284

Neurosurgery Service

- +2204 Causalgia: A Study of Sympathetic Activity in Affected Patients (FY-73 T).
2205 Clinical Data Acquisition Project. A Grant Application. (FY-78 T). 285

Ophthalmology Service

- 2304 Technician-Assisted and Computer-Assisted Ophthalmology Care (FY-75 T). 286
2306 Clinical Quantification of Intraocular Malignant Melanoma Volume (FY-76 O). 288
2307 Evaluation of 0.1% Dipivalyl Epinephrine (DPE or GSH 1226) in the Treatment of Glaucoma (FY-77 C). 289
2308 Scleral Buckling for Retinal Detachment 1973-1976. A Retrospective View (FY-78 O). 295
2309 A Study of Eye Trauma and Treatment in the Military (FY-78 PO). 296
2310 Intraocular Lens (FY-78 O). 298

Otolaryngology Service

- 2508 An Experimental Analysis of Aural Rehabilitation Using Programmed Instructions (FY-70 T). 299
2510 A Multidimensional Assessment of Stuttering Severity (FY-76 PC). 300
2512 Effects of Hearing Impairment and Acoustic Filtering on the Perception of Speech (FY-76 PO). 306
2516 The Effect of Amplification on Limited High-Frequency Hearing Loss (FY-77 PO). 308
2517 Evaluation of a Specialized Technique for Training Audiovisual Integration in Hard-of-Hearing Patients (FY-78 PO). 310

DEPARTMENT OF SURGERY (continued)

	<u>Page</u>
<u>Otolaryngology Service</u>	
2518 The Effects of Analytic Training on the Sentence Recognition Ability of Hearing-Impaired Soldiers (FY-78 PO).	313
2519 An Investigation of the Effects of Several Competing Signals on Aided Hearing Performance (FY-78 C).	315
2520 The Effect of the Change of Body Position on Nystagmus Induced by Bithermal Caloric Irrigation and on Spontaneous Nystagmus during Electronystagmography (FY-78 O).	317
2521 Reaction Times of Stutterers and Nonstutterers (FY-78 O).	318
2522 Monaural Versus Binaural Amplification for Hearing Impaired Listeners (FY-78 O).	320
2523 The Relationship between Electroacoustic Parameters and Perceived Sound Quality of Hearing Aids (FY-78 PO).	321
2524 The Effects of Assertiveness Training on Hearing Impaired Soldiers (FY-78 O).	323
2525 Generation and Evaluation of Synthetic Facial Images for Studying and Training Lipreading (FY-78 O).	324
<u>Renal Transplant Service)</u>	
2601 In Vivo and In Vitro Properties of Sensitized Lymphocytes in Transplantation Immunology (FY-72 PT).	326
2610 Antilymphocyte Globulin (ALG) and Kidney Transplantation: A Controlled Double Blind Study (FY-73 O).	327
2611 Survey of Multiparous Patients for Anti-HLA Antibodies (FY-76 T).	
2614 HLA Tissue Typing Studies on an Alaskan Population Group, and Possible Relationship to Organ Transplantation Science (FY-77 T).	329
2615 Immunological Monitoring of the Transplant Recipient (FY-78 O).	330
2616 Obviating the Graft Versus Host Reaction (FY-78 O).	331

DEPARTMENT OF SURGERY (continued)

	<u>Page</u>
<u>Thoracic Surgery and Cardiovascular Service</u>	
2703 Exclusive Use of Autologous Blood Transfusions (Auto-transfusions) in Elective Thoracic and Open Heart Surgical Procedures (FY-75 C).	332
<u>Urology Service</u>	
2804 An Evaluation of the Efficacy of Tadenan in the Treatment of Benign Prostatic Hyperlasia (FY-76 O).	334
2805 Biochemical Studies of Urinary Polyamines in Human Genitourinary Carcinoma (FY-76 PO).	335
2807 Determination of Human Prostatic Acid Phosphatase in both Benign and Malignant Conditions by Radioimmunoassay (FY-77 PO)	336
2809 Relationships between Prostatic Cancer and Excretion of Urinary Cholesterol (FY-78 PO).	339
2810 Comparative Study of High Dose (5000 Rads) Versus Low Dose (2000 Rads) Preoperative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder (FY-78 O).	340
<u>Allergy and Rheumatology Service</u>	
3102 Therapy of Immunodeficiency Diseases with Transfer Factor (FY-73 PC).	341
3103 Techniques for the Detection of Anti-Nuclear Antibodies. A Comparative Study (FY-73 T).	342
3105 An Evaluation of Immunologic Response in Ragweed-Sensitive Patients by New Techniques (FY-73 PC).	350
3109 Complement Deficiencies of their Relationship to Diseases in Man (FY-73 PC).	352
3111 Quantitative Serum IgE in Human Infections, Immune Deficiency States and Diseases with Impaired Cellular Immunity (FY-73 T).	354
3113 Synovial Fluid Analysis in Rheumatic Disease (FY-73 T).	356
3117 Evaluation and Study of Patients with Primary and Secondard Immunodeficiency Disease (FY-73 C).	363

<u>Allergy and Rheumatology Service (continued)</u>		<u>Page</u>
3123	Study Immune Mechanisms in Systemic Lupus Erythematosus (FY-75 PT).	365
3138	Immunologic Mechanisms of Cutaneous Reactions to Inhalant Allergens (FY-76 PO).	373
3139	Immunologic Function of Human Tonsil and Adenoid Cells (FY-77 C).	374
3140	Hyposensitization: Long Term Sequelae (FY-77 PC).	375
3141	A Multiclinic Long Term Comparative Efficacy and Safety Study of Albuterol Versus Isoproterenol Nebulizer Solution (by Hand Bulb Nebulizer) in the Treatment of Reversible Obstructive Airway Disease in Adults (FY-77 PT).	377
3143	Biologic (Skin Testing) Potency of Allergenic Extract Reference Preparations (FY-77 PT).	378
3144	Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma (FY-77 PO).	380
3145	A Fluorescent Test for Extractable Nuclear Antigen (FY-77 O).	383
3146	Immunotherapy Kit Potency Persistence (FY-77 O).	386
3147	An Evaluation of the Safety and Efficacy of Allergen Immunotherapy with Hymenoptera Venom in Insect Sting Allergic Patients (FY-77 PO).	387
3148	The Histologic Evaluation of Diffuse Lung Disease in Sjogren's Syndrome by Transbronchial Lung Biopsy (FY-78 O).	389
3149	Investigation of Immunologic Imbalance in Atopic Dermatitis (FY-78 PO).	392
3150	Comparison of Two Licensed Commercially Available Short Ragweed Extracts Differing in their Ability to Meet the Bureau of Biologics Proposed Criteria of Potency (FY-78 C).	395
3151	Allergic Disease Center Study of Hymenoptera Insect Venom as an Agent for Diagnosis (FY-78 O).	396

<u>Allergy and Rheumatology Services (continued)</u>		<u>Page</u>
3152	Factors Affecting the Theophylline Half Life (FY-78 O).	397
3154	WRMC #7802, Evaluation of Prostaglandin Producing Suppressor Cells in Cancer Patients (FY-78 O).	399
 <u>DEPARTMENT OF OBSTETRICS AND GYNECOLOGY</u>		
4106	Post-Operative Treatment of Women with Resectable Ovarian Cancer with Radiotherapy Alkeran or No Further Treatment (FY-70 C).	400
4113	Cooperative Gynecologic-Oncology Group (FY-72 O).	401
4116	The Evaluation of Fetal Systolic Time Intervals and Beat to Beat Interval Variations in Fetal Heart Rate as Early Indicators of Fetal Maturity and Fetal Distress (FY-75 O).	402
4124	Fetal Intensive Care Monitoring in a Long-Range Continuing Project (FY-73 O).	403
4126	The Clinical Evaluation of a Rapid Method for Pre-surgical Cleansing of the Hands (FY-75 T).	404
4129	Antepartum Fetal Evaluation of Noise Evoked Fetal Heart Rate Response as an Indicator of Fetal Well Being. (FY-74 O).	405
4132	A Clinical Study to Evaluate the Efficacy of Prophylactic Antibiotics in Reducing the Morbidity Associated with Cesarean Section (FY-77 PC).	407
4134	Treatment of Women with Cervical Cancer Stage IIB, IIIB, IVA, Confined to the Pelvis and/or Para-Aortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) (Phase II) (FY-77 O).	408
4135	A Randomized Comparison of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylmelamine and Melphalan in Patients with Ovarian Adenocarcinoma: Suboptimal Stage III, Stage IV, and Recurrent, Equivalent to Stage III and IV (Phase III). (FY-77 O).	409

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

		<u>Page</u>
4136	A Randomized Comparison of Melphalan Alone Versus Melphalan Therapy Plus Immunotherapy (Corynebacterium Parvum) in the Treatment of Women with Stage III (Optimal) Epithelial Carcinoma of the Ovary (Phase II) (FY-77 O).	410
4137	A Randomized Comparison of Pelvic and Abdominal Radiation Therapy Versus Pelvic Radiation and Melphalan Versus Melphalan Alone in Stage II Carcinoma of the Ovary (Phase III) (FY-77 O).	411
4138	Diagnosis and Treatment of Intrauterine Abnormalities Using the Hysteroscope (FY-78 O).	412
4139	A Randomized Comparison of Melphan, 5-Fluorouracil and Megace Versus Adriamycin, Cytosan, 5-Fluorouracil and Megace in the Treatment of Patients with Primary Stage III, Primary Stage IV, Recurrent or Residual Endometrial Carcinoma (Phase III) (FY-77 O).	413
4140	A Clinical-Pathologic Study of Stage I and Stage II Carcinoma of the Endometrium (FY-78 O).	414
4141	A Randomized Study of Adriamycin as an Adjuvant after Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma Stage I and Occult Stage II (FY-78 O).	415

DEPARTMENT OF RADIOLOGY

Nuclear Medicine Service

4501	Clinical Evaluation of Fluorescence Scanning of the Thyroid with an Americium 241 Source (FY-73 PO).	416
4502	Plasma Angiotension Levels and Response to Anti-hypertensive Therapy in Essential Hypertension (FY-73 C).	417
4514	Clinical Evaluation of Indium-III DTPA (FY-75 O).	418
4515	Broad Clinical Evaluation of ^{99m} Techetium Labelled Stannous Glucoheptonate as a Diagnostic Agent for Studying the Kidney (FY-75 C).	419
4518	Clinical Evaluation of ^{99m} Techetium Electrolytically Labelled Human Serum Albumin for Injection ^{99m} Tc(E) HSA (FY-76 C).	420

DEPARTMENT OF RADIOLOGY

Page

Nuclear Medicine Service

- 4519 Study of Thallium Chloride TL 201 for Myocardial Imaging in Acute Infarction and/or Ischemia (FY-77 C). 421

Radiation Therapy Service

- 4601 Participation in the National Cooperative Study of Early Hodgkin's Disease (FY-69 PO). 422

DEPARTMENT OF PATHOLOGY

Blood Bank

- 5501 Incidence of Hemolytic Disease of the Newborn Due to ABO Incompatibility (ABO/HDN) (FY-77 PC). 425

DEPARTMENT OF PEDIATRICS

- *6009 Clinical and Laboratory Investigation of Meningeal Leukemia (FY-75 T) 558
- *6013 Evaluation of Four Modes of Therapy of Reye's Syndrome, Acute Encephalopathy with Fatty Infiltration of the Viscera: A Multi-Hospital Study (FY-75 T). 559
- *6014 Granulocyte Transfusion by Two Methods: Continuous Flow Centrifugation and Filtration Leukapheresis (FY-76 T). 560
- 6017 Clinical Studies in Thermometry (FY-77 T). 426
- 6018 Newborn Host Defenses: I. Developmental Aspects of Newborn Neutrophil Chemotaxis (FY-77 PO). 427
- 6021 The Role of Luteinizing Hormone Releasing (LHRH) in Evaluation of the Hypothalamic Pituitary Gonadal Axis in Children (FY-78 O). 429

<u>DEPARTMENT OF PEDIATRICS</u>		<u>Page</u>
6023	Newborn Host Defenses II. Studies of the Newborn Neutrophil Membrane Using Lectins as Molecular Probes (FY-78 PO).	431
6024	Newborn Host Defenses: III. Phagocytosis and Killing of Group B Streptococci (FY-78 PO).	433
6025	Role of Surface Tension Measurement of Amniotic Fluid Lipid Extract in Prediction of Development in RDS Neonates (FY-78 O).	434
6026	Tracheal Aspirate Surface Tension as a Prognostic Indicator in Infants with Respiratory Distress Syndrome (RDS) (FY-78 O).	485
<u>DEPARTMENT OF NEUROLOGY</u>		
7105	Study of CEP Responses in Pediatric Epileptic Patients before and after Withdrawal of Anticonvulsants (FY-72 T).	436
7109	The Application of Somatosensory Spinal Evoked Response in Spinal Cord Pathology (FY-76 T).	437
<u>DEPARTMENT OF PSYCHIATRY</u>		
7111	Interruption of Maintenance Neuroleptic Therapy (FY-76 O).	438
7151	Cognitive Components of Interpersonal Functioning in Brain Damaged Adults (FY-78 C).	439
7212	RBC Lithium Concentration and Clinical Correlates (FY-77 T).	440
7214	Pre- and Post-Discharge Assessment of Psychiatric Patients (FY-77 O).	441
7215	Neuroendocrine Correlates in Depressive Disorders (FY-78 T).	442
7217	Management of Impairment of Accommodations Secondary to Psychotropic Medication (FY-78 O).	443

FOOD SERVICE DIVISIONPage

- 8001 The Effect of a Diet Controlled in Lactose, Gluten,
Fat and Residue on Female Oncology Patients Receiving
Abdominal Radiation Treatment (FY-77 PC). 444

USA DENTAL ACTIVITIES (DENTAC)

- 8027 Clinical Evaluation of Freeze-Dried Bone Allografts 446
in the Treatment of Severe Periodontal Osseous
Defects (FY-76 C).
- 8029 The Effect of Patient Applied Fluoride on Bacterial 448
Plaque and Gingivitis (FY-77 O).

DIVISION OF MEDICINE, WRAIR

- 8050 Immunity to Measles in a Military Population (FY-77 T). 450

DEPARTMENT OF HEMATOLOGY, WRAIR

- 9009 Abnormalities of B6 Metabolism and Glycogen Metabolism 451
in Hodgkin's Disease (FY-75 O).
- 9010 Vitamin B6 Metabolism in the Hematopoietic System of 455
Patients Receiving Isoniazid and Patients with Sidero-
blastic Anemia (FY-75 O).
- 9012 The Effect of Infectious Hepatitis on Erythroid Colony 456
Formation by the Plasma Clot Culture Method (FY-77 O).
- 9013 The Carbohydrate Dependence of Platelet Surface In- 458
teractions in Hypercoagulable Stress (FY-77 O)
- 9014 Dengue Fever Virus and Human Monocyte Interactions 460
(FY-77 O).
- 9015 The Effect of Pyridoxine Administration on Red Cell 462
Metabolism of Vitamin B₆ and the Oxygen-Affinity
of Hemoglobin (FY-78 O).
- 9016 Investigation of Pyridoxine as a Treatment for Sick 463
Hemoglobinopathies (FY-78 PO).
- 9017 Treatment of Sick Cell Anemia with Pyridoxine (FY- 465
78 O).
- 9018 De Novo Synthesis of Purine Nucleotides in Human 466
Erythrocyte Precursors (FY-78 O).

<u>GASTROENTEROLOGY SERVICE, WRAIR</u>		<u>Page</u>
9025	Functional Characterization of Human Intestinal Lymphocytes in Gastrointestinal Disorders (FY-77 T).	471
<u>NURSING SERVICE, WRAIR</u>		
9027	Relationship of Vital Signs to Cardiac/Respiratory Arrest (FY-77 C).	475
<u>NURSING SERVICE, WRAMC</u>		
9031	The Effect of Prenatal Teaching on Breast Feeding (FY-77 T).	484
<u>AFIP</u>		
9035	Effects of Altitude, Mood and Dietary Habits on Performance of Choice-Reaction Time Task (FY-77 O).	500
9036	Urease and Deaminases in Chemistry and Medicine (FY-77 PO).	502
*9037	Women's Knowledge of Breast Cancer and Breast Self-Examination (FY-77 C).	562
<u>NEUROPSYCHIATRY, WRAIR</u>		
9077	Peripheral Neuropathy and Chronic Obstructive Lung Disease. A Clinical and Electrophysiological Study (FY-77 O).	503
9078	Encephalopathy Following Treatment of Chronic Pulmonary Failure: A Clinical and Electroencephalographic Study (FY-77 T).	504
<u>USAIDR</u>		
9090	The Effects of Immunosuppressant on the Oral Environment (FY-76 T).	505
9091	Candida Shifts and pH Changes in Patients with Oral Malignancies (FY-76 T).	506
9094	Utilization of Biodegradable Copolymers of Polylactic and Polyglycolic Acid (FY-77 O).	507
* Investigators late in turning in Annual Progress Report.		
+ Investigators did not turn in an Annual Progress Report.		
WR 70-1	Clinical Investigation Program, WRAMC	509
Author Index		549

Unit Summary Sheet

Clinical Investigation Service, WRAMC

This Annual Progress Report is for the Fiscal Year 1978.

1. Mission Changes

During FY-78 the Service was expanded to include the Infectious Disease Laboratory from WRAIR. This laboratory consists of three technical personnel and equipment and has several active protocols. Currently these personnel are operating in two laboratory areas, Room 2B26 in the NMTF and a laboratory still located in the WRAIR.

2. Personnel Actions, Current Strength

(a) Personnel transferred from WRAIR to WRAMC with the Infectious Disease Laboratory:

Dobek, Arthur	GS-12	0403
Ciak, Jennie	GS-12	0403
Dickson, Edward	GS-09	0404

(b) Personnel hired on temporary appointment to provide support to investigative projects:

Londono, Sonnya	GS-07	0644	
Gemski, Judith	GS-05	0645	
Hirte, Linda	GS-07		(Appointment Expired)

(c) Current Manpower

<u>Description</u>	<u>Grade</u>	<u>MOS</u>	<u>Br</u>	<u>Actual</u>	<u>Name</u>
C, Clin Invest Svc	06	61F9B	MC	1	Evans
Asst C, Clin Invest Svc	04	61F9B	MC	1	Boehm
Lab Officer (Admin)	03	68F9D	MSC	1	Reed
Biochemist	02	68C	MSC	1	Bongiovanni
Dietitian	02	3420	AMS	1	Ramos
Med Lab Tech	E7	92B	AMED	1	Price
Med Lab SP	E5	92B	AMED	1	Dutton
Med Lab SP	E4	92B	AMED	2	Dickinson Balthazard
Science & Eng	E4	01H20	AMED	1	Byrne
Supv Rsch Chemist	14	1320	GS	1	Bruton
Microbiologist	12	0403	GS	1	Dobek
Microbiologist	12	0403	GS	1	Ciak
Chemist	11	1320	GS	1	Smith
Supv Biologist	11	0401	GS	1	Davis

<u>Description</u>	<u>Grade</u>	<u>MOS</u>	<u>Br</u>	<u>Actual</u>	<u>Name</u>
Supv Bio Tech	10	0404	GS	1	Young
Physiologist	11	0413	GS	1	Wright
Physiologist	11	0413	GS	1	Lukes
Med Tech	09	0645	GS	1	Armstrong
Med Tech	09	0645	GS	1	Burgess
Chemist	09	1320	GS	1	Dawson
Chemist	09	1320	GS	1	Maydonovitch
Bio Lab Tech	09	0404	GS	1	Dickson
Bio Lab Tech	09	0404	GS	1	Butler
Bio Lab Tech	08	0404	GS	1	Coleman
Med Tech	07	0645	GS	1	Barnes
Med Tech	07	0645	GS	1	Bongiovanni
Med Tech	07	0645	GS	1	Londono
Secy Steno	06	0318	GS	1	Ervin
Clk, DMT	05	0316	GS	1	Laster
Clk, DMT	05	0316	GS	1	Legere
Clk, DMT	04	0316	GS	1	Roberts
Clk, DMT	04	0316	GS	1	McAnally
Clk, DMT	04	0316	GS	1	Kendall
Med Tech (Chemist)	04	0645	GS	1	Martin

3. Investigative Program Summary

Number of active protocols	291
Number of completed protocols	94
Number of publications	82
Number of presentations	36

4. Incentives

(a) The Commander, WRAMC, provided this Service with \$17,200 to support personnel who participated in the Clinical Investigation Program and had papers or exhibits accepted for presentation at various national scientific meetings. Forty five investigators utilized this support during FY-78.

(b) Allocations of operating funds for both supplies and equipment has become extremely tight. The Chief, CIS, and his staff are constantly reviewing protocol progress, cost analysis is regularly conducted to determine which projects merit funding.

(c) The Biochemistry Laboratory is in full operation and provides investigative projects with sophisticated chemical procedures that were previously unavailable.

34

(d) The Bailey K. Ashford Medal for outstanding investigative work by a resident was awarded to William D. Bellville, MAJ MC, Urology Service, during graduation ceremonies for 1978 for his work in urology related to the measurement of prostatic acid phosphatase by radioimmunoassay.

(e) The Service provides funding for reprints of articles published in the scientific media by the staff at WRAMC.

5. Objectives:

(a) To achieve continuous improvement in the quality of patient care through a program of relevant clinical investigation.

(b) To furnish the future backbone of the Army Medical Department with experience in the mental discipline associated with proper utilization of the scientific method and organized inquiry.

(c) To further develop and refine the research environment necessary for Walter Reed to continue in its standing as an accredited center for advanced training in the health care sciences.

6. Technical Approach: Provides direction and management as outlined under provisions of AR 40-38, Clinical Investigation Program; AR 40-7, Use of Investigational Drugs in Humans; and WRAMC Regulation 70-1, Clinical Investigation Program, WRAMC. Provides guidance, assistance and support to the house staff on matters pertaining to the program. Coordinates the WRAMC program with higher headquarters and other facilities.

7. Funding, FY-78:

Civilian Personnel	\$492,761
Military Personnel	287,076
Travel	17,200
Rental	18,000
Contracts	44,000
Supplies	314,000
Average Cost/Protocol	5,213

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34

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9

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DEPARTMENT OF PEDIATRICS

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Work Unit: 1004

Title: Stress Ulceration in the Medical ICU: Incidence and Possible Prevention with Cimetidine.

Investigators:

Principal investigator: David A. Peura, M.D.

Co-investigator: Lawrence F. Johnson, M.D.

Objective: To prove in a double blind randomized control fashion if Cimetidine is effective in decreasing the incidence of stress induced gastrointestinal hemorrhage in the Medical Intensive Care Unit.

Technical Approach: See protocol.

Progress and Results: To date, 30 patients have been studied under the technical design of the protocol. Since the study is a double blind randomized study, the code has not been broken and it is impossible at this time to determine if Cimetidine is more active than the placebo in preventing stress ulceration. The initial desire of the protocol was to have 100 patients studies, however, it is felt that after 50 patients are adequately evaluated, an impartial observer will break the code and analyze the data to see if statistically significant results have been attained.

Conclusions: Thirty patients have been studied under the protocol, but because of its double blind randomized nature and the code has not been broken, results of efficacy of Cimetidine versus placebo are not available at this time. It is anticipated that 20 more patients will be evaluated and impartial observer will then analyze the data, breaking the code to determine if statistical significance has been reached. Should statistical significance not be obtained with the 50 patients, the study will be continued to its duration of 100 patients.

Funds Utilized, FY 78: None.

Funds Requested, FY 79: Same as initial protocol.

Publications: None to date.

Type of Report: Interim.

Investigational Drug Progress Report

Program Work Unit: 1004

Title: Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine.

Investigators:

Principal investigator: David A. Peura, M.D.

Co-investigator: Lawrence F. Johnson, M.D.

Study is conducted in the Medicine Service, Walter Reed Army Medical Center.

Thirty subjects have been studied to date with no evidence of adverse reaction. Because the study is a double blind randomized study, the code has not been broken, and the effectiveness of Cimetidine over that of placebo is not available at this time. It is anticipated that 20 more patients will be evaluated and an impartial observer will break the code and evaluate the data to see if statistical significance has been reached. Should the data not indicate statistical significance at the 50 patient mark, the study will be continued until the original group of 100 patients is evaluated.

As per requirements by FDA, on site inspection has been carried out by Smith, Kline and French Laboratory, sponsors of the clinical investigation project, and inventory of medication has been kept in the Walter Reed AMC Pharmacy, and interim collaboration of inventory has been performed by representatives of Smith, Kline and French.

1. Work Unit Number 1112
2. Project Title: Use of Minoxidil in the Treatment of Severe, Uncontrolled or Poorly Controlled Hypertension.
3. Principal Investigator: Daniel A. Nash, Jr., LTC, MC
Associates: Jeffery C. Weidig, MAJ, MC
Suzanne M. Bergman, MAJ, MC
Khalidoun A. Nsouli, MAJ, MC
Chester A. Amedia, MAJ, MC
Christopher W. Old, CPT, MC
Jack Moore, CPT, MC
Michael Siedlecki, CPT, MC
4. Objective: To assess the efficiency and safety of Minoxidil in severe hypertension refractory to currently available potent anti-hypertensive agents.
5. Technical Approach: Patients who are determined to be unresponsive to standard antihypertensive drugs with persistent, severe hypertension are selected for treatment with Minoxidil. The response of their hypertension to the therapy, consequential complications, intercurrent events, etc. are followed very closely. This is an uncontrolled study with results based on data from our unit and from numerous other collaborators around the country and reported as clinical experience.
6. Progress and Results: Since this protocol was initiated at Walter Reed Army Medical Center, sixteen patients have been treated with Minoxidil when all other agents failed to control their hypertension. The thirteen entered prior to the past year have been previously commented upon, two of which continue to be doing well on the agent. In the past year three new patients have been started on Minoxidil. Each responded to the agent with improved blood pressure control. One patient no longer requires the agent in view of improved blood pressure control with renal transplantation. The other two are doing well on the agent at two months and at one month.
7. Conclusion: Minoxidil is a potent agent that is effective when other agents in use are not. Side effects and intolerance have not been limiting factors in the use of this agent in our small series. On a broader scale the preliminary results from collateral groups also appear to be favorable toward the effectiveness and tolerance of the agent. This is suggested by the apparent acceptance of the agent by the Food and Drug Administration anticipated to occur during the next year.
8. Funds Utilized FY 78: None
9. Fund Requirements FY 79: None
10. Publications: None
11. Type of Report: Interim

DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-MN

SUBJECT Terminated Report Clinical Investigation Program
Work Unit #1120, Bone Marrow Reserve and White Blood
Count Survival in Patients With Chronic Renal Failure

TO THRU: Ch, Dept of Medicine FROM Ch, Nephrology Svc

DATE 12 Sept 1978 CMT 1
NASH/mkb/62319

TO: Ch, Clinical Investigation Svc

1. Work Unit #1120, with Project Title - Bone Marrow Reserve and WBC Survival in Patients With Chronic Renal Failure was terminated as a Walter Reed Army Medical Center Nephrology Service program prior to the present Fiscal Year.
2. The principal investigator Major J. P. Johnson, MC is no longer assigned to Walter Reed Army Medical Center. No members of the Walter Reed Army Medical Center Nephrology Service wish to continue the project.
3. There have been no expenditures by the Nephrology Service in the prior year on this project. To our knowledge, there have been no presentations or publications of work related to this project.



DANIEL A. NASH, JR., MD

LTC, MC

Chief, Nephrology Service

Walter Reed Army Medical Center

1. Work Unit No. 1121
2. Project Title: Combined Prednisone and Cytoxan Therapy Coupled with Plasma Exchange in the Treatment of Antiglomerular Basement Membrane Mediated Renal Disease.
3. Investigators: Principal - John P. Johnson, MAJ, MC
Associates - Jack Moore, CPT, MC
Daniel A. Nash, Jr., LTC, MC
4. Objective: To compare the effect of Prednisone and Cytoxan alone and in combination with plasma exchange on the rate of disappearance of circulatory anti-glomerular basement membrane antibody and the effect of this on modifying disease course.
5. Technical Approach: Patients with confirmed anti-GMB antibody mediated renal disease will be randomized to treatment with either Prednisone and Cytoxan alone or in combination with plasma exchange. Disappearance rates of antibody will be calculated and compared along with clinical outcome and response to therapy.
6. Progress and Results: Ten patients have been entered into the study. Three have received plasma phoresis in addition to Cytoxan and Prednisone. Disappearance rates of antibody have been observed. Initial observations suggest the rate of disappearance may be similar between the two groups. However, the patient experience remains too small at this time for meaningful comparisons.
7. Conclusions: Only tentative conclusions can be reached at this time. As indicated above, more patients are required in each treatment group for significant comparison of relevant parameters and outcome to be made.
8. Funds Utilized: FY-78 - None
9. Fund Requirements FY 79: Personnel - None
Equipment - None
Supplies - None
Travel - \$600.00
Others - None
10. Publications: None
11. Type of Report: Interim

1. Work Unit No. 1122
2. Project Title: Evaluation of Urinary Creatinine Excretion as a Reference Point for Comparing Total Body Potassium Determinations.
3. Investigators: Principal - Donald E. Butkus, COL, MC
Associate - Daniel A. Nash, Jr., LTC, MC
4. Objective: To determine a more reliable reference standard with which to compare total body potassium measurements and to increase the usefulness of this measurement in assessing body potassium stores.
5. Technical Approach: Ambulatory volunteers who are receiving no medication and who have normal plasma potassium concentrations will have total body potassium measurements performed in a total body counter measuring naturally occurring K^{40} and no isotopes will be administered. Volunteers will collect 24-hour urine samples for creatinine and have blood drawn for measurement of plasma and red cell potassium concentrations. Total body potassium measurements will be expressed per gram of creatinine excreted, and results will be compared with standard references including height, weight, body surface area and standard predictive formulæ.
6. Progress and Results: To date fifteen males and three females have been evaluated completely in accord with the protocol. The standard range in variation for those tested has been determined. It appears at this time to be considerable variation with the techniques employed.
7. Conclusions: There appears to be only fair agreement using this technique with those results available in the literature and by the methods mentioned above. However, the data base is far too small for sound conclusions at this time.
8. Funds Utilized FY-78: Supplies - \$500.00
9. Funds Requested FY-79: Personnel - None
Equipment - None
Supplies - \$500.00
Travel - \$600.00
Others - None
10. Publications: None
11. Type of Report: Interim

1. Work Unit Number 1123
2. Project Title: Effect of Acidosis, Nutritional Status and Aldosterone on Potassium Metabolism in Patients with Stable Chronic Renal Failure.
3. Investigators: Principal - Donald E. Butkus, COL, MC
Associates - Suzanne M. Bergman, MAJ, MC
Daniel A. Nash, Jr., LTC, MC
4. Objective: To access body potassium stores in patients with chronic renal failure and relate deficits to three potential causes - acidosis, nutritional status and status of mineralocorticoid production.
5. Technical Approach: Patients with stable chronic renal failure will be studied in conjunction with routine hospitalization to determine total body status by total body counting of endogenous K^{40} . No radioisotopes will be administered. Total body potassium status will be related to patients degree of systemic acidosis, nutritional intake and plasma aldosterone levels. Following detection of total body potassium deficits serial measurements will be made to assess the effect of correction of acidosis and/or nutritional status.
6. Progress and Results: To date a very small group of normal individuals have been studied in conjunction with a similar protocol to act as baseline controls for normal values of K^{40} . These values have been shown to be variable. Two chronic renal failure patients have undergone the protocol evaluation.
7. Conclusions: The results determined to date have shown such variability that interpretations by the techniques employed have been shown to be very difficult. Further, there has been limited patient participation and physician interest in this protocol. Both of these factors indicate that continuation of this protocol would be wasteful.
8. Funds Utilized FY 78: Personnel - None
Equipment - None
Supplies - \$2000.00
Travel - None
Other - None
9. Funding Requested FY 79: None
10. Publications: FY 78 - None
11. Type of Report: Terminated (Project and funding account should be terminated immediately.)

1. Work Unit #1124
2. Project Title: The Effect of Hyperuricemia on Chronic Renal Failure
3. Investigators: Principal: Daniel A. Nash, Jr., LTC, MC
Associate: None
4. Objective: To determine if hyperuricemia occurring in chronic renal failure is an aggravating factor to residual renal function.
5. Technical Approach: Randomized controlled evaluation in which patients do or do not have their serum uric acid concentrations normalized with the drug Allopurinol as they approach end-stage renal disease. The consequential courses of these two groups are compared.
6. Progress and Results: To date, three patients have been entered into the study. Both that were placed on Allopurinol had side effects and the drug had to be discontinued after follow-up periods of five months and two months.
7. Conclusions: Preliminary conclusions are that the side effects of Allopurinol might limit its application to the treatment of hyperuricemia in end-stage renal disease on a wide scale basis.
8. Funds Utilized, FY-78 - None
9. Fund Requirements, FY-79
 - Personnel: None
 - Equipment: None
 - Supplies: None
 - Travel: \$500.00
 - Other: None
10. Publications: None
11. Type of Report: Interim

Work Unit No.: 1212

Title of Project: Computer Assisted System for Coronary Artery Disease (CASCADE)

Investigators:

Principal:

Patrick J. Lawrence, MD
LTC, MC, WRAMC

Associates:

P. Richard Zarda, Ph.D.
Max Rabinowitz, M.D.
Julius L. Pedynek, Jr., M.D., Ph.D., COL MC
Sarendra K. Dhir, Ph.D.
Hugh McAllister, M.D., LTC MC
Samuel Goodloe, M.D., LTC MC

Objectives:

- a. Establish a method of computer quantification of the degree of coronary obstruction using standard coronary arteriograms.
- b. Establish the precision and validity of the method by comparing computer measurements of arteriograms of coronary models and specially injected postmortem human hearts.
- c. Utilize the foregoing to predict hemodynamic parameters, such as pressure gradients and flows across coronary obstructions.

Technical Approach:

- a. Program the computer at David Taylor Naval Ship Research and Development Center to model the geometry of coronary artery lesions from standard cineangiograms performed on patients in the catheterization laboratory at WRAMC.
- b. Verify the accuracy of the method using metal models of lesions as well as animal and postmortem human hearts injected with radiodense gelatin which can be studied microscopically after sectioning.
- c. Use these models to predict hemodynamic parameters associated with coronary artery lesions.

Progress and Results: Very little progress has been made due to delays in funding and equipment installation as well as transfer of three of the Investigators. The final installation of the computer equipment in the WRAMC catheterization laboratory should be complete in February 1979. Work may begin at that time on programming the computers.

Conclusions: Pending funds utilized, FY-78: None

Funding Requirements, FY-79:

a. Personnel (DTNSRDC Analyst time)	\$ 34,000.00
b. Equipment (Manometers, catheters)	250.00
c. Consumable Supplies (Injection materials for hearts)	250.00
d. Travel (Presentation at clinical meetings)	1,000.00
e. Modification of Facilities	
f. Other (Computer time)	<u>5,000.00</u>
	\$41,500.00

Publications: None

Type of Report: Interim

Work Unit No: 1213

Title of Project: Electron Microscopic Evaluation of Cardiovascular
Guidewires

Investigators: Patrick J. Lawrence, MD
LTC, MC, WRAMC

Frank B. Johnson, MD
Chief, Dept. Chemical Pathology, AFIP

Objective: To examine cardiovascular guidewires with scanning electron microscope to look for defects in the Teflon coating which may be caused by the catheterization procedure.

Technical Approach: Selected guidewires from cardiac catheterizations done at WRAMC will be investigated using the Scanning Electron Microscope at AFIP.

Progress and Results: Approximately twenty guidewires have been examined. No conclusions have been reached as of this writing.

Conclusions: None at present.

Funds Utilized, FY-78: None

Funding Requirements, FY-79:

Personnel:	None
Equipment:	None
Supplies:	\$249.00 (photographic)
Travel:	500.00
Other:	250.00 (reprint cost)
Total	\$999.00

Publications: None

Type of Report: Interim

Work Unit No.: #1308

Title of Project: Inderal Kinetics in Hyperthyroidism

Investigators:

Principal: Kenneth D. Burman

Associates: Leonard Wartofsky

Dave Lowenthal

Objectives: To assess Inderal half-life in thyrotoxic patients.

Technical Approach: All patients are studied on Ward 47. They are given Inderal and blood samples are obtained to ascertain its disappearance rate.

Progress & Results: About 15 patients have been analyzed and preliminary data indicates that the half life of Inderal may be about 90 minutes which is not different than a group of normal controls. Dr. Lowenthal has moved his laboratory twice in the last two years and believes now he can help finish this project.

Conclusions: Inderal half-life is about one hour.

Funtis Utilized FY-78:

Approximately \$500.00

Funds Requested FY-79: None

Work Unit No.: 1310

Title of Project: TRH in Patients with Hypothalamic Pituitary Thyroid Disease

Investigators:

Principal: Leonard Wartofsky, LTC, MC

Associates: R.C. Dimond, MAJ, MC, M. Schaaf, M.D.

Objectives: To assess the response to synthetic TRH (Thyrotropin releasing hormone) in various suspected endocrine disorders.

Technical Approach: Patients are studied on the metabolic ward. Blood samples are drawn for measurement of thyrotropin prolactin, and other hormones, before and after the injection of 100-500 mcg of synthetic TRH. Until Dec 1976, the latter agent was an investigational drug but has since been released for clinical use.

Progress & Results: Approximately 500 such studies have been completed in approximately 300 subjects. Although much of the data is yet to be analyzed, some appears in the publications listed below.

Conclusions: TRH has been found to be a useful agent for the assessment of disorders of the hypothalamic-pituitary-thyroid axis, with minimal or negligible side effects or problems associated with its use; and has also proved to be a valuable research tool.

Funds Utilized FY-78:

Funds Requested FY-79:

1100 Personnel	2895
2100 Travel	600
2319 Rental	100
2400 Print. & Repro.	750
2572 Contractual Svcs.	2000
2600 Cons. Supplies	750
3100 Non-Exp. Equip.	500
MEDCASE	8595

- Publications:
1. Wartofsky, L., et al., Estimates of Pituitary Stores of TSH and PRL in Normal and Hypothyroid Subjects by Use of Continuous TRH Infusion, Advances in Thyroid Research, Excerpta Medica, pp. 268-271, 1976.
 2. Wartofsky, L., et al., Effect of Acute Increases in Serum T₃ on TSH and PRL Responses to TRH, J Clin Endocrinol & Metab, 42:451-466, 1976.
 3. Wartofsky, L., et al., Nature of Thyroidal Suppression and TSH and PRL Responses to TRH during Experimental Malaria in Man, J Clin Endocrinol & Metab, 44:85-90, 1977.

Type of Report: Interim

Work Unit No.: #1311

Title of Project: Treatment of Thyroid Storm with anion Exchange Resin.

Investigators:

Principal: Kenneth D. Burman

Objective: Thyroid storm is serious that can be characterized by excessive circulating levels of T3 and T4. The purpose of this protocol is to allow us for appropriation to decrease T4 levels by an exchange using a resin which has been effective in dogs.

Progress & Results: All studies to date have been performed in dogs and show that the level of T3 and T4 is quite effective by use of this anti exchange resin.

Funds Utilized FY-78:

None

Funds Requested FY-79:

None

Publications:

Burman, K.D., Yeager, Driggs, Earll, and Wartofsky. JCEM 42-70, 1976.

Type of report: Interim.

Work Unit No.: 1314

Title of Project: Stimulation and Suppression of Plasma Prolactin in Patients with Pituitary Disease

Investigators:

Principal: Gordon L. Noel, MAJ, MC

Associates: Leonard Wartofsky, LTC, MC, Marcus Schaaf, M.D.,
J.M. Earll, COL, MC

- Objectives:
1. To evaluate the efficacy of various tests now available in stimulating and suppressing the release of prolactin as a means of assessing pituitary function.
 2. To study the pathophysiology of abnormal prolactin secretion in various forms of galactorrhea.
 3. To ascertain whether prolactin has osmoregulatory properties in patients with disorders of prolactin secretion.

Technical Approach: Patients with pituitary tumors and/or galactorrhea have complete evaluation of their pituitary function by standard methods (thyroid and adrenal function studies, growth hormone stimulation and suppression). Following this, tests of prolactin release (TRH test, chlorpromazine stimulation, breast stimulation, sleep and of prolactin suppression (L-dopa, water loading) are performed.

Progress & Results: As indicated in the progress report for 1977, a study of 29 patients with galactorrhea and/or pituitary tumors reveal that basal prolactin determinations correlated better with the presence of a pituitary tumor than all of the stimulatory and suppressive manipulations. A small but statistically significant rise in mean prolactin was found in 10 normal men and 11 normal women one half hour after ingestion of a water load. There was no effect of intravenous infusion of either hypotonic or hypertonic saline. Water loading was shown to also have no effect on elevated TSH and PRL levels or the response to TRH in patients with primary hypothyroidism. Additional studies of TSH and prolactin responses to TRH in patients with a variety of disorders such as amenorrhea-galactorrhea, renal failure, and thyroid disease are in varying stages of completion and the data is yet to be analyzed.

Conclusions: From those experiments that have been completed, we can conclude that basal prolactin concentrations are more useful than other methods of differentiating between tumorous and non-tumorous galactorrhea. TRH and chlorpromazine testing are effective means of establishing the integrity of the pituitary and hypothalamic pituitary interactions. Water loading studies did not support a physiologic role for prolactin in the short term regulation of plasma osmolality in normal or hypothyroid subjects.

Funding Utilized FY-78:

Funding Requested FY-79: None

1100 Personnel
2100 Travel
2319 Rental
2400 Printing & Reprod.
2572 Contractual Svcs.
2600 Consumable Supplies
3100 Non-Expendable Equip.
MEDCASE

Publications: None in Fiscal Year 78

Type of Report: Terminated

Work Unit Number: 1320

Title of Project: Effect of Lilly Compound 83636 on Plasma Prolactin in Humans

Investigators:

Principal: Jerry M. Earll, M.D., COL, MC

Associates: Marcus Schaaf, M.D.
Andrew G. Frantz, Columbia Presbyterian Medical Center, Chief of Physicians and Surgeons, Columbia University, New York

- Objectives:
- 1) To study the ability of Lilly Compound 83636 (Lergotrile Myselate) to lower growth hormone and prolactin and to improve clinical manifestations in patients with pituitary tumors causing acromegaly.
 - 2) To study the growth hormone & prolactin response to TRH before and during Lergotrile treatment.

Technical Approach: Patients with acromegaly were hospitalized on the Kyle Metabolic Unit on a constant calcium intake. Blood specimens for growth hormone and prolactin measurements were obtained before treatment with Lergotrile during a standard TRH test and on another day every 2 hours for a 24-hour period of unrestricted ward activity. Blood specimens for growth hormone and prolactin measurements were also obtained over a 3 hour period following the initial dose of Lergotrile, 0.5 mg orally, and again 3 and 7 days later as the dose was gradually increased to 1.0 mg and 2.0 mg. TRH test and blood sampling every 2 hours over a 24 hour period was repeated on full dosage, 2.0 mg every 8 hours orally. Clinical parameters of growth hormone activity (nerve conduction, ring size, hand volume and urinary calcium excretion) were measured before and during Lergotrile. Some patients were discharged to continue the drug as outpatients with re-evaluation at 2 to 4 week intervals.

Progress & Results: Twelve acromegalic patients have been studied. Lergotrile caused a 66-96% reduction in growth hormone by 2 1/2 hours at each dosage increment in most of the patients. The TRH response of growth hormone was not modified by Lergotrile. Multiple sampling every 2 hours over a 24-hour period indicated significant reduction in growth hormone, but the short half life of the drug did not result in continuous suppression.

Conclusion: Lilly Compound 83636 (Lergotrile Myselate) may be useful in selected acromegalic patients. This medication is not approved for long term therapy of acromegaly.

Publications: Kleinberg, DL, Schaaf, M, Frantz, AG: Studies with Lergotrile Mesylate in Acromegaly. Fed Proc 37:2198-2201, 1978.

Type of Report: Terminated

Work Unit Number: 1321

Title of Project: Effects of Cancer Chemotherapy Agents on Endocrine Function

Investigators:

Principal: COL Jerry M. Earll, MC

Associates: None

Objectives: To evaluate the effects of modern cancer chemotherapy on endocrine function.

Technical Approach: Patients receiving standard protocol approved drugs have their endocrine function tested before and after treatment. No change is made in the patients usual management for malignancy.

Progress and Results: Five patients have had evaluation of their adrenal function following completion of either one or two courses of chemotherapy. Two other patients had been entered in the study but became ill with hepatitis. No significant suppression of adrenal function was detected following the early courses of chemotherapy. A pronounced hyperzincuria occurred within 24 hours of the administration of most chemotherapeutic agents while serum zinc levels remained stable.

Conclusions: Preliminary results suggest minimal if any significant impairment of adrenal function following initial courses of chemotherapy. The immediate hyperzincuria following certain chemotherapeutic agents may reflect drug toxicity upon tumor and normal tissue cells at a time much sooner than traditional concepts would suggest. The principal investigator changed duty positions two years ago and it has not been possible to make further progress on this project. Furthermore, during this interval there has been a great deal of published new information from other investigators concerning endocrine function during cancer chemotherapy. In view of this, it is requested that this project be terminated.

Work Unit No.: 1329

Title of Project: Lithium Effects on Thyroid

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if lithium levels influence thyroid conversion.

Technical Approach: Lithium is administered to patients with T3, T4 and rT3 levels measured.

Progress & Results: 10 patients have been studied. It has been determined that lithium does influence thyroidal conversion.

Conclusions: Lithium does influence thyroidal conversion.

Funds Utilized, FY-78: 2600 Consumable supplies \$9639.37

Funding Requirement, FY-79:

Personnel
Travel
Rental
Printing & Reproduction
Contractual Svcs.
Consumable supplies
Non-expendable equipment
MEDCASE

TOTAL

Publications: JCEM,

Type of report: Interim

Work Unit No.: 1331

Title of Project: Effect of Iodine and Lithium on the Release of
Thyroxine from the Thyroid Gland of Patients with
Thyrotoxicosis

Investigators:

Principal: Timothy M. Boehm, MAJ MC

Associates: Kenneth D. Burman, MAJ MC
Leonard Wartofsky, LTC MC

Progress and Results: Twenty-one patients have completed study. Lithium and iodine are comparably efficacious agents in blocking thyroidal release. Additional therapeutic benefit was observed if lithium was added to iodine therapy but not if iodine was added to lithium. This "conditional" synergism was observed regardless of whether methimazole was employed. Three additional patients received iodine during both treatment periods; no additional decrease in release was seen during the second iodine treatment period, ruling out a cumulative iodine effect as the origin of the "conditional" synergism seen when lithium was added to iodine.

Conclusions: None as yet.

Funding Utilized, FY-78: None specifically. Only one patient was studied during FY-78, and no specific funding was necessary.

Funding Requested, FY-79: None at present.

Publications: A manuscript is under revision. An abstract was presented at the annual meeting of the Endocrine Society, Chicago, 1977.

Type of Report: Interim

Work Unit: 1332

Title of Project: Differentiation of Benign from Malignant Thyroid Nodules:
Assessment of New Diagnostic Techniques.

Investigators:

Principal: Charles Smith, MAJ, MC

Associates: Leonard Wartofsky, LTC, MC, Prentice Thompson, LTC, MC
Robert Kaminski, MAJ, MC

Objectives: To attempt to differentiate benign from malignant thyroid nodules by use of the routine I¹³¹ and Technetium ^{99m} scans plus newer diagnostic techniques including ultrasonography, fluorescent scanning and needle biopsy.

Technical Approach: 50-75 patients with solitary thyroid nodules will have the diagnostic tests mentioned under objectives which will be correlated with findings at surgery in hope of reducing the number of patients requiring the latter.

Progress & Results: To date, 61 patients have been included in this study and thus far 40 patients have gone to surgery. The results of all studies obtained during this protocol and tissue pathologic reports on the surgical specimens are at present being collated and examined. While this data is being evaluated, it is anticipated that an additional 15-25 patients will be entered into the study during the next fiscal year.

Conclusions: None as yet.

Funds Utilized FY-78: Consumable Supplies 2600 103.50

Funds Requested FY-79:

1100 Personnel	280
2100 Travel	
2319 Rental	100
2400 Printing & Repro.	1000
2572 Contractual Svcs.	500
2600 Cons. Supplies	500
3100 Non-Expendable Equip.	250
MEDCASE	2630

Publications: None

Type of Report: Interim

Work Unit No.: 1334

Title of Project: Regulation of extra thyroidal conversion of
Thyroxine (T4) to Triiodothyronine (T3).

Investigator:

Principal: Kenneth D. Burman

Objective: To determine the factors regulating conversion of T4 to T3.

Technical Approach: Patients are administered T4 in the amount of T3
generated are determined.

Progress & Results: 10 patients have been studied, and it has been
determined that T4 levels do not influence conversion of T4 to T3.

Conclusions: Thyroid hormone levels do not influence conversion to T4
to T3.

Funds Utilized, FY-78: 2600 Consumable supplies 667.00

Funding Requirement, FY-79:

Personnel
Travel
Rental
Printing & Reproduction
Contractual Svcs.
Consumable supplies
Non-expendable equipment
MEDCASE

TOTAL

Publications: American Federation of Clinical Research, May 1976.

Type of Project: Interim.

Work Unit No.: 1336

Title of Project: Effects of Continuous Infusion of TRH on Growth Hormone Secretion in Acromegaly.

Investigators:

Principal: Richard C. Dimond, MD, LTC, MC

Associates: D. Corrigan, MD, L. Wartofsky, MD, LTC, MC

Objective: To examine the pattern of growth hormone secretion in patients with acromegaly during continuous infusion of TRH.

Technical Approach: TRH was administered intravenously by constant infusion at a rate of 1 mcg/min for 4 hours and then by a 500 mg bolus injection; blood samples were obtained serially. Total growth hormone concentration was measured by radioimmunoassay; immunochemical components of circulating growth hormone was measured by a combination of gel chromatography and radioimmunoassay.

Progress and Results: Only four patients have been studied; therefore, the data are incomplete and insufficient to draw any definite conclusions. The preliminary data suggest that growth hormone secretion can be stimulated continuously by TRH administered by this technique in certain acromegalic patients. No untoward events were experienced by any of the patients participating in this study. Due to the limited number of new patients available for entry into the protocol, this study has been terminated.

Conclusions: None.

Funds Utilized, FY-78: None.

Funding Requirements, FY-79: None.

Publications: None.

Type of Report: Terminated.

Work Unit No.: 1337

Title of Project: Growth Hormone Response to TRH in Acromegaly.

Investigators:

Principal: Richard C. Dimond, MD, LTC, MC

Associates: D. Corrigan, MD, L. Wartofsky, MD, LTC, MC,
M. Schaaf, MD, and J. M. Earll, MD, COL, MC

Objectives: To assess the inhibiting effects of thyroid hormone, glucose, and L-Dopa on the abnormal growth hormone response to TRH in acromegaly.

Technical Approach: Standard TRH stimulation tests after administration of thyroid hormone, after administration of L-Dopa, and during a constant intravenous infusion of glucose. Blood samples were obtained serially, and growth hormone concentration was measured by radioimmunoassay.

Progress and Results: Only five patients have been studied; therefore the data are incomplete and insufficient to draw any definite conclusions. The preliminary data suggest that prior administration of thyroid hormone, L-Dopa, or glucose do not block the growth hormone secretory response to TRH in certain acromegalic patients. No untoward events were experienced by any of the patients participating in this study. Due to the limited number of new patients available for entry into the protocol, this study has been terminated.

Conclusions: None.

Funds Utilized, FY-78: None.

Funding Requirements, FY-79: None.

Publications: None.

Type of Report: Terminated.

Work Unit Number: 1338

Title of Project: Hormonal and Metabolic Changes in Hypertension

INVESTIGATORS:

Principal: Jerry M. Earll, M.D.

Associate: Marcus Schaaf, M.D.

Objectives: Normal and low renin group of hypertensive patients would be studied metabolically to determine if there were any alterations of body composition suggestive of "Unidentified" mineral corticoid substances.

Technical Approach: Hypertension patients would receive a standard workup with careful screening to categorize them as to whether they were normal or low renin groups. The low renin patients were to be matched carefully by age to a normal renin hypertension patient. Whole body composition with emphasis on potassium determinations in a whole body counter were to be made. Five hypertension patients have been studied. Difficulty has been encountered in obtaining the low renin hypertension group for study. Six patients had basal prolactin levels studied while on low salt and high salt diets and following diuretic stimulation. There was no significant change in basal prolactin during these manipulations. Difficulty with operation of the whole body counter and changing priorities in the department restricted any further progress.

Conclusion: In spite of some animal evidence to indicate that prolactin may be an important hormone in manipulating salt and water metabolism, major changes in sodium intake have failed to stimulate or suppress prolactin. The principal investigator changed his duty position two years previously and it has not been possible to continue active research on this project. Request that this project be terminated.

Work Unit No.: 1339

Title of Project: Effect of Lithium on Intrathyroidal Iodine Content.

Investigator: Timothy M. Boehm, MAJ MC

Objective: To ascertain whether chronic lithium therapy in psychiatric patients alters intrathyroidal iodine.

Technical Approach: To utilize the fluorescent scanner to measure intrathyroidal iodine content in patients receiving lithium therapy.

Progress and Results: Preliminary studies have been completed in three patients; apparently some patients receiving chronic lithium have elevated intrathyroidal iodine. The pace of the study has been slowed because of the limited availability of psychiatric patients, and no further patients were entered onto the study in FY-78.

Conclusions: None

Funds Utilized, FY-78: None

Publications: None

Type of Report: Terminated

Work Unit No.: 1340

Title of Project: Use of Fluorescent Thyroid Scanning to evaluate Iodine Kinetics during Propylthiouracil Therapy of Graves Disease.

Principal Investigator: Charles Smith, MAJ, MC

Associate Investigators: Leonard Wartofsky, LTC, MC, Kenneth D. Burman, MAJ, MC
Robert Kaminski, MAJ, MC

Objective: To utilize the fluorescent thyroid scanner to quantitate and follow alterations in thyroidal iodine content during antithyroid therapy of Graves' disease.

Technical Approach: Ten to 20 patients with Graves' disease are to be studied.

The following tests will be performed weekly throughout the study: serum thyroxine (T₄), serum triiodothyronine (T₃), resin uptake of triiodothyronine (T₃RU), serum iodide (I_s), thyroidal ¹²⁷I (I_t) by fluorescent scan. In addition, two twenty four hour urines/week will be collected and twenty four hour iodide excretion (I_u) determined. At the end of each study period a perchlorate discharge test (Cl₂) will be performed.

Basal determinations of Entry into study: T₄, T₃, T₃RU, I_s, I_t, I_u, Cl₂

Study Period I: Propylthiouracil 150 mg/day
weekly: T₄, T₃, T₃RU, I_s, I_t, I_u
Study period ends when weekly studies are stable; Cl₂ at end of study period.

Study Period II: Propylthiouracil 450 mg/day
Study period ends when weekly studies are stable; Cl₂ at end of study period.

Study Period III: Propylthiouracil 1200 mg/day
Study period ends when weekly studies are stable; Cl₂ at end of study period.

Study Period IV: Identical to Study Period III except
5 drops SSKI tid
Study ends at one week

Progress & Results: Six patients have been studied to date and the data is presently being evaluated. Attempts are being made to recruit additional patients, although it is anticipated that there will be some delay due to the absence of the principal investigator who is on temporary duty elsewhere. Studies will resume in early 1979.

Conclusions: None as yet.

Funds Utilized FY-78: Consumable Supplies \$2,637.00

Funds Requested FY-79:

1100	Personnel	1200
2100	Travel	400
2319	Rental	200
2400	Print. & Repro.	400
2572	Contractual Svcs.	1000
2600	Cons. Supplies	1000
3100	Non-Expendable Equip.	250
Medcase		<u>4450</u>

Publications: None

Type of Report: Interim

Work Unit Number: 1342

Title of Project: Dietary Influence on Prolactin Secretion

Investigators:

Principal: Jerry M. Earll, COL, MC

Associates: Marcus Schaaf, M.D., Kenneth Burman, MAJ, MC

Objectives: To evaluate changes in hormone secretion during alterations of carbohydrate and fat in the diet. Emphasis is being placed upon prolactin, growth hormone and thyroid hormone changes.

Technical Approach: Obese patients will be admitted to the metabolic ward where baseline studies will be performed prior to a high fat and low carbohydrate diet. Following these dietary manipulations, some patients will undergo fasting episodes.

Progress and Results: Principal investigator changed duty positions forcing this project into a very low priority. No progress has been made during the past year. Request this project be terminated.

Work Unit No.: 1345

Title of Project: Conversion of testosterone estradiol

Investigator:

Principal: Kenneth D. Burman

Objective: To determine conversion rates of testosterone and estradiol on patients with Klinefelter's Syndrome.

Technical Approach: Patients with Klinefelter's Syndrome are administered testosterone and the amount of estradiol measured .

Progress & Results: Patients studied.

Conclusions: None.

Funds Utilized, FY-78:

Funding Requirement, FY-79:

Personnel	3,000
Travel	300
Rental	
Printing & Reproduction	
Contractual Sccs.	200
Consumable supplies	1,500
Non-e endable equipment	
MEDCASE	
TOTAL	<hr/> \$6,800

Publications: None.

Type of report: Interim.

Work Unit No.: 1346

Title of Project: Thyroid Function Tests in Cord Blood Maternal Serum Fluid.

Investigator:

Principal: Kenneth D. Burman

Objective: To measure thyroid hormone levels in cord blood maternal serum and amniotic fluid.

Technical Approach: Cord blood and amniotic fluid are obtained at term deliveries and thyroid hormone levels determined.

Progress & Results: Reverse T3 levels increase in cord blood and also in amniotic fluid.

Conclusions: Thyroid hormone metabolism is altered in Fetal Maternal Unit.

Funds Utilized, FY-78:

Funding Requirement, FY-79:

Personnel	3,693
Travel	
Rental	
Printing & Reproduction	400
Contractual Svcs.	
Consumable supplies	5,000
Non-expendable equipment	
MEDCASE	
 TOTAL	 \$9,093

Publications: JCEM, April 1976

Type of report:Interm

Work Unit No.: 1347

Title of Project: Investigations into the physiology of L-Reverse
T-3 (rT3) and -3-'Diodothyronine (3-3'T2)

Investigator:

Principal: Kenneth D. Burman

Objective: To determine states in which rt3 and 3,3'T2 are altered.

Technical Approach: Serum is measured for 3,3'T2 and rT3 in metabolic states.

Progress & Results: RT3 is increased in fasting, and in various metabolic states and 3,3'T2 levels do not increase during fasting.

Conclusions: The diet seems to influence thyrcid hormone metabolism.

Funds Utilized, FY-78: 2600 Consumable supplies \$31,946.64

Funding Requirment, FY-79:

Personnel	13,000
Travel	500
Rental	
Printing & Reproduction	500
Contractual Svcs.	
Consumable supplies	15,000
Non-expendable equipment	
MEDCASE	
 TOTAL	 \$29,000

Publications:

Type of report: Interim.

Work Unit No.: 1348

Title of Project: Correlation of Dose and Duration of Exogenous Steroid Therapy with Recovery of Hypothalamic-Pituitary-Adrenal Function

Investigators:

Principal: Timothy M. Boehm, MAJ MC

Associate: Joseph Bruton, PhD

Objectives: To investigate the effect of high dose steroid therapy of less than one month duration in inducing hypothalamic pituitary suppression, as reflected by ACTH responsiveness.

Technical Approach: To use metyrapone and insulin tolerance testing, with measurement of plasma cortisol and ACTH, as a measure of hypothalamic-pituitary suppression.

Progress and Results: Preliminary studies have been completed in one patient, and laboratory verification of the ACTH assay is pending. Insufficient accrual of patients was obtained, and resources are not available now on Kyle Metabolic Unit to perform the necessary assays.

Conclusions: None at present.

Funds Utilized FY-78: None

Funds Requested FY-79: None

Publications: None

Type of Report: Final

Work Unit No.: 1349

Title of Project: Evaluation of the Use of a Specific Radioimmunoassay
for Compound S in the Interpretation of the Results
of Metyrapone Testing.

Investigator: Timothy M. Boehm, MAJ MC

Progress and Results: Approximately 100 patients and 10 normals were
under study. Data is presently under analysis.

Conclusions: There is some discordance between urine and plasma re-
sponses to metyrapone. It is unclear, however, whether
urine or plasma responses correlate better with clinical
evidence of ACTH deficiency.

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications: None

Type of Report: Final

Work Unit No.: 1351

Title of Project: Effects of Cyproheptadine on Pituitary Secretion.

Investigators:

Principal: Richard C. Dimond, MD, LTC, MC

Associates: R. C. Smallridge, MD, MAJ, MC, L. Wartofsky, MD, LTC, MC,
and J. M. Earll, MD, COL, MC.

Objective: To examine the role of serotonin on the regulation of prolactin and TSH secretion in patients with hyperprolactinemia, galactorrhea, or hypothyroidism.

Technical Approach: Standard TRH tests before and after three days of treatment with cyproheptadine, 4 ng p.o. t.i.d.

Progress and Results: Due to logistic problems, no studies of nocturnal hormonal secretion during sleep with continuous EEG monitoring were performed. TRH tests before and after cyproheptadine were performed in only two patients. Therefore, insufficient data are available to draw any conclusions. No untoward events were experienced by the patients participating in this study. Since the protocol cannot be carried out as originally designed, this study has been terminated.

Conclusions: None.

Funds Utilized, FY-78: None.

Funding Requirements, FY-79: None.

Publications: None.

Type of Report: Terminated.

Work Unit No.: 1352

Title: Echocardiographic Findings in Acromegaly

Investigators:

Principal: Robert C. Smallridge

Associates: Sal Rajfer
James Davia
Marcus Schaaf

Objective: To evaluate the incidence of asymmetric septal hypertrophy in patients with acromegaly.

Technical Approach: Echocardiograms were obtained with an Ekoline 20A (Smith Kline Instrument, Philadelphia, PA) using a 2.25 mega Herz transducer with a 1.4 cm diameter and a 10cm focus. The echocardiograms were recorded using M-mode scans on an Irex Continutrace Multichannel strip chart recorder (Irex Medical Systems Ossining, NY), with the patients supine or rotated slightly to the left. The left ventricular septal and posterior wall dimensions were measured at the peak of the R wave of a simultaneously recorded electrocardiogram. Left ventricular function was assessed by calculating the systolic dimensional shortening of the minor axis of the ventricular chamber. This was determined by the formula $\frac{EDD-ESD}{EDD}$, where EDD is the end-diastolic left ventricular diameter measured at the peak of the R wave and ESD is the end-systolic diameter at the time of maximal anterior movement of the posterior wall. Comparison of group means for systolic dimensional shortening was made by simple one-way analysis of variance.

Progress & Results: Twenty-seven patients with acromegaly had echocardiograms performed to delineate the ventricular septum, left ventricular posterior wall (LVPW), and mitral valve. Left ventricular function was assessed by calculating the systolic internal dimensional shortening (IDS) of the left ventricle. Six patients met the criteria for asymmetric septal hypertrophy (ASH) and eight had concentric left ventricular hypertrophy (LVH). The remaining 13 patients were categorized as "normal", although 6 had septal measurements >11 mm. The ASH group had significantly greater % IDS during systole than the normal group ($p < 0.05$) and the LVH group ($p < 0.01$). Initial mean growth hormone levels were considerably higher in the LVH than in the normal group (93 vs. 34 ng/ml).

Conclusions: Echocardiographic abnormalities are common in acromegaly, and patients with ASH and acromegaly appear to have significantly increased ventricular ejection. Many of the patients with LVH have no evidence of clinical cardiovascular disease, and their LVH may be related to higher initial growth hormone levels.

Funds Utilized, FY-78:

None Consumable Supplies 2600

Supplies:

Travel:

Personnel:

Equipment:

Other:

Funds Utilized, FY-79:

Personnel;	1100	300
Print & Reprod.	2400	150
Travel:		

Supplies:

Equipment:	TOTAL	\$ <u>450</u>
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Other:

- Publications:
1. Smallridge, R.C., S. Rajfer, J. Davia, and M. Schaaf, Acromegaly and the heart, an echocardiographic study Clin Res 26 (3): 312A, 1978.
 2. Smallridge, R.C., S. Rajfer, J. Davia, and M. Schaaf, Acromegaly and the heart, an echocardiographic study, Amer J Med (in press).

Type of report: Completed.

Work Unit No.: 1353

Title of Project: The regulation of T4 conversion, grant proposal.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine the effect of regulating T4 conversion.

Technical Approach: Various human and animal studies are determined in giving T4 isotope and determining how much is converted in T3 and T4 metabolic states.

Progress & Results: It has been determined that the low of T4 does not influence T3 conversion.

Conclusions: Thyroid hormone levels do not change the level of conversion.

Funds Utilized, FY-78: 2600 Consumable supplies \$968.23

Funding Requirement: FY-79:

Personnel	18,000
Travel	200
Rental	
Printing & Reproduction	250
Contractual Svcs.	
Consumable supplies	12,500
Non-expendable equipment	2,000
MEDCASE	
TOTAL	<u>\$32,950</u>

Publications: Burman, K.D., American Federation of Clinical Research, May 1976.

Type of report: Interim.

DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is The Adjutant General's Office.

REFERENCE OR OFFICE SYMBOL

HSWP-ME

SUBJECT

Comments of Dr. Bridenbaugh Concerning Protocols 1353 and 1359 and 1360 Progress Reports

TO C, Clin Invest Svc

FROM Kenneth D. Burman, M.D. DATE 25 April 79 CMT 1
Burman/lmm/6-1417

1. With regard to annual progress report for work unit 1353 entitled "The Regulation of T₄ Conversion, Grant Proposal". Dr. Bridenbaugh suggests that it be clearer if progress is being made on the protocol and if the progress report indicates substantial deviation from the original protocol. Specifically, fourteen patients have been studied on this protocol, given varying doses of Synthroid and measuring serum T₄ and T₃ conversion. Our results unequivocally indicate that the percentage of conversion is constant regardless of the T₄ level i.e., the serum T₄ level may be elevated but a conversion of always approximately 20% exists. None of the patients had any unexpected side effects. The funding requested for this protocol included \$18,000.00 for personnel. This study is still in progress but it has taken approximately a year and a half of one technicians time to measure the serum T₄, T₃'s and do the numerous isotopic studies involved. The remaining questions involve (1) does the level of T₄ determine conversion to lesser iodothyronines (2) what tissues are important in converting T₄ to T₃ and what process is being regulated by this and (3) is the enzyme that converts T₄ to T₃ influenced by T₄ levels.

2. Concerning Dr. Bridenbaugh's comments on work unit 1359 entitled "The Effect of Reverse T₃ and T₂ on Thyroidal Secretion". Approximately ten patients have been studied, there has been no deviation from the original protocol and there have been no side effects whatsoever from this protocol. The results have not reached statistical significance yet and it is expected that approximately ten more patients need to be studied. It does appear, however, that reverse T₃ administration does not influence thyroidal secretion.

3. Concerning Dr. Bridenbaugh's comments on work unit 1360 entitled "Investigations Concerning T₃ Production Rates". Approximately ten patients have been studied and we have compared cold infusions of iodothyronine vs labeled infusions. An abstract has been accepted for presentation at the annual meeting of the Endocrine Society. Our results indicate that both infusions give similar results. There has been no deviation from the original protocol and there have been no unexpected or adverse side effects. Statistical significance between the different groups of patients have not been reached and it is expected that another five to ten patients will be studied.



KENNETH D. BURMAN, M.D.
MAJ, MC
Endocrine-Metabolic Service

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Work Unit No.: 1354

Title of Project: Purification of Testosterone-Estradiol Binding Globulin.

Investigators:

Principal: Robert A. Vigersky, MD, MAJ, MC

Objectives: To purify and characterize estradiol binding globulin in order to 1) study physiologic effects of steroid binding on target tissue function; and 2) develop a radioimmunoassay.

Technical Approach: Use of serial purification methods e.g., preparative polyacrylamide gel electrophoresis, affinity chromatography, temperature dependent affinity chromatography, and isotachopheresis.

Progress & Results: Due to lack of a technician, this project has not been started.

Conclusions: None.

Funds Utilized, FY-78:

2600 Consumable Supplies

Funding Requirement FY-79: (Grant from USUHS. Funds requested from CIS).

Personnel	3,400
Supplies, general	3,850
Non-expendable; loose issue	
Printing, publication	500
Rental	200
Animals	
Isotopes	
Equipment	
Travel	600
TOTAL	<hr/> \$3,550

Publications: None.

Type of report: Interim.

Work Unit No.: 1355

Title of Project: The Effect of Short-Term, High-Dose Steroid upon
Thyroidal Release in Thyrotoxicosis.

Investigator: Timothy M. Boehm, MAJ MC

Progress and Results: Three patients have completed study. Serious questions have arisen regarding the validity of the double isotope technique as a measure of thyroidal release. In addition, other protocols involving thyrotoxic patients have been assigned a higher priority.

Conclusions: None

Funds Utilized, FY-78: None

Funds Requested, FY-78: None at present

Publications: None

Type of Report: Interim

Work Unit No.: 1356

Title of Project: The Pituitary-Gonadal Axis and Testicular Functions
in Hyperthyroidism

Investigators:

Principal: Robert A. Vigersky, MD, MAJ, MC
Gerald S. Kidd, MD, MAJ, MC

Associates: Kenneth D. Burman, MD, MAJ, MC
Joseph Bruton, Ph.D.
Leonard Wartofsky, MD, LTC, MC
Allan R. Glass, MD, MAJ, MC

Objective: To assess the status of the pituitary-gonadal axis and the status of spermatogenesis in men with hyperthyroidism.

Technical Approach: Measurement of basal levels of total and free testosterone and estradiol, LH, FSH and testosterone-estradiol binding globulin while hyperthyroid and after euthyroidism has been maintained for 3 months. Semen analysis is performed on 3 occasions at both time periods. The pituitary reserve of LH and FSH is determined by their response to 100 ug of LRH at both time periods and the testosterone synthetic reserve is determined at both time periods by a 4 day hCG (human chorionic gonadotropin-4000 U, intramuscularly a day) test.

Progress & Results: Seven patients have been studied. Four of 6 who had semen analysis had low total sperm counts. The group demonstrated partial Leydig cell failure and an inverse correlation of total sperm count and plasma estradiol concentration. These are all new observations. Abnormal feedback regulation of gonadotropins was evident. Follow-up studies have not been completed.

Conclusions: Men with hyperthyroidism have abnormalities of gonadal function involving the Leydig cell, seminiferous tubules, and the pituitary-testicular axis.

Funds Utilized, FY-78:

Personnel	4,118
Supplies	1,532
Printing, Audio-Visual	1,000
Misc., Xerox, etc.	250
Contract Labs.	2,000
Consultants	250
Non-exp. supplies	250
Equipment	
Travel	
TOTAL	<hr/> \$ 9,400

Funds Requested, FY-79:

Personnel	4,850
Supplies	3,600

Misc, Xerox, etc	250
Contracts	2,300
Rental	200
Non-exp. supplies	
Equipment	
Travel	400

TOTAL

\$11,600

Publications: Vigersky, R.A., Kidd, G.S., Dawson, E., and Bruton, J. "Testicular Function in Thyrotoxic Men", Abst. 851, Endocrine Society, June 1978.

Kidd, G.S., Glass, A.R., Vigersky, R.A., "The Hypothalamic-Pituitary-Testicular Axis in Thyrotoxicosis", submitted to J. Clin. Endo. Metab., September 1978.

Type of report: Interim.

Work Unit No.: 1357

Title of Project: Effect of T3 and rT3 on Extracellular
Cyclic Nucleotide Levels in Humans.

Investigators:

Principal: H. Linton Wray, M.D., LTC, MC

Associates: Kenneth D. Burman, M.D., MAJ, MC
Robert C. Smallridge, M.D., MAJ, MC
Leonard Wartofsky, M.D., LTC, MC

Objective: To determine if, in humans, urine and plasma levels of cyclic AMP and cyclic GMP are changed by administration of 3,5,3'triiodothyronine (T3) and 3,3',5'triiodothyronine (reverse T3, rT3).

Technical Approach: Hypothyroid patients will be studied before, during and after taking T3, rT3 or both T3 and rT3. Hyperthyroid patients will be studied only with rT3. Patients will be studied for 12 days: 3 days of baseline, 6 days of treatment and 3 days of post-treatment. Plasma cyclic AMP and cyclic GMP and serum T3, rT3 and T4 will be measured on days 1-5 and 8-12.

Progress & Results: Too few patients have been studied to give meaningful results because suitable volunteers have been used in other research protocols.

Conclusions: The interest in and the importance of this study has not waned and it should be more active in FY-79.

Funds Utilized FY-78:

2600	Supplies	800
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Funds Requested FY-79:

1100	Personnel	4,050
2100	Travel	400
2319	Rental	200
2400	Print & Repro.	450
2572	Contract Svc.	-
2600	Consumable supplies	2,700
3100	Non-exp. equipment	950
	Medicare	-

\$8,750

Publications: None

Type of report: Interim

Work Unit No.: 1358

Title of Project: The affect of obesity and fasting on T3 receptors in circulating mononuclear cells.

Investigator: Kenneth D. Burman

Principal:

Objective: To determine if T3 receptors in white cells age during fasting.

Technical Approach: White cells are isolated and their receptor number determined in Fed and Fasting patients.

Progress & Results: After several months the method has been developed to measure T3 receptors and studies are beginning.

Conclusions: None.

Funds Utilized, FY-78;

None.

Funding Requirement, FY-79:

Personnel	3,000
Travel	
Rental	
Printing & Reproduction	500
Contractual Svcs.	
Consumable supplies	4,000
Non-expendable equipment	
MEDCASE	
TOTAL	<u>\$7,500</u>

Publications: None.

Type of report: Interim.

Work Unit No.: 1359

Title of Project: The effect of rT3 and 3,3'T2 on Thyroid Secretion, T4 degradation Iodide leak and Thyrotoxic patients.

Investigator:

Principal: Kenneth D. Burman
Timothy Boehm

Objective: To determine if rT3 administration influences thyroid secretion in degradation.

Technical Approach: rT3 is administered to patients with Thyroxic and T4 clearance rates determined.

Progress & Results: RT3 does not appear to influence T4 degradation.

Conclusions: None.

Funds Utilized, FY-78: 2600 Consumable supplies \$41,80

Funding Requirement, FY-79:

Personnel	3,000
Travel	600
Rental	
Printing & Reproduction	500
Contractual Svcs.	
Consumable supplies	5,000
Non-expendable equipment	
MEDCASE	
TOTAL	<hr/> \$ 9,100

Publications: In progress.

Type of report: Interim

DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is The Adjutant General's Office.

REFERENCE OR OFFICE SYMBOL

HSWP-ME

SUBJECT

Comments of Dr. Bridenbaugh Concerning Protocols 1353 and 1359 and 1360 Progress Reports

TO C, Clin Invest Svc

FROM Kenneth D. Burman, M.D. DATE 25 April 79

CMT 1

Burman/lmm/6-1417

1. With regard to annual progress report for work unit 1353 entitled "The Regulation of T₄ Conversion, Grant Proposal". Dr. Bridenbaugh suggests that it be clearer if progress is being made on the protocol and if the progress report indicates substantial deviation from the original protocol. Specifically, fourteen patients have been studied on this protocol, given varying doses of Synthroid and measuring serum T₄ and T₃ conversion. Our results unequivocally indicate that the percentage of conversion is constant regardless of the T₄ level i.e., the serum T₄ level may be elevated but a conversion of always approximately 20% exists. None of the patients had any unexpected side effects. The funding requested for this protocol included \$18,000.00 for personnel. This study is still in progress but it has taken approximately a year and a half of one technicians time to measure the serum T₄, T₃'s and do the numerous isotopic studies involved. The remaining questions involve (1) does the level of T₄ determine conversion to lesser iodothyronines (2) what tissues are important in converting T₄ to T₃ and what process is being regulated by this and (3) is the enzyme that converts T₄ to T₃ influenced by T₄ levels.

2. Concerning Dr. Bridenbaugh's comments on work unit 1359 entitled "The Effect of Reverse T₃ and T₂ on Thyroidal Secretion". Approximately ten patients have been studied, there has been no deviation from the original protocol and there have been no side effects whatsoever from this protocol. The results have not reached statistical significance yet and it is expected that approximately ten more patients need to be studied. It does appear, however, that reverse T₃ administration does not influence thyroidal secretion.

3. Concerning Dr. Bridenbaugh's comments on work unit 1360 entitled "Investigations Concerning T₃ Production Rates". Approximately ten patients have been studied and we have compared cold infusions of iodothyronine vs labeled infusions. An abstract has been accepted for presentation at the annual meeting of the Endocrine Society. Our results indicate that both infusions give similar results. There has been no deviation from the original protocol and there have been no unexpected or adverse side effects. Statistical significance between the different groups of patients have not been reached and it is expected that another five to ten patients will be studied.



KENNETH D. BURMAN, M.D.

MAJ, MC

Endocrine-Metabolic Service

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Work Unit No.: 1360

Title of Project: Investigations concerning T3 production rates.

Investigators:

Principal: Kenneth D. Burman

Objective: To determine if T3 production rates are the same determined by isotopic and cold unlabeled hormone methods.

Technical Approach: I-125, T3 and unlabeled T3 administered to patients and clearance rates determined.

Progress & Results: It has been determined that these 2 methods give similar results for clearance and production rates.

Conclusions: Same as above.

Funds Utilized, FY-78:

None.

Funding Requirement, FY-79:

Personnel

Travel

500

Rental

Printing & Reproduction

Contractual Svcs.

Consumable supplies

1,000

Non-expendable equipment

MEDCASE

TOTAL

\$1,500

Publications: In preparation.

Type of report: Interim

Work Unit Number: 1361

Title of Project: Postoperative changes in free testosterone and sex-hormone-binding-globulin

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if the fall in total serum testosterone that occurs after surgical stress is associated with concomitant changes in free testosterone and sex-hormone-binding-globulin

Technical Approach: Obtaining blood samples serially from patients undergoing elective surgery and measurement of serum hormones by appropriate methods.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Twelve patients having surgery under general anesthesia and six patients having surgery under spinal or local anesthesia have been studied. In patients having general anesthesia, free testosterone falls concomitantly with total testosterone, though plasma LH and FSH do not change. Plasma 17-OH-progesterone, androstenedione, and estradiol also appear to fall after surgery. Development of an assay for sex-hormone-binding-globulin is ongoing to facilitate completion of this project. A paper on this subject has been accepted for publication by Fertility and Sterility.

Funds Utilized, FY-78: 2600 Consumable supplies 2,357.50

Funding Requirement, FY-79:

Personnel	1,500
Travel	600
Rental	200
Printing & Publication	2,500
Contractural svcs.	1,000
Supplies	
Non-expendable equipment	

TOTAL	<hr/> \$5,800
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Work Unit No.: 1362

Title of Project: Medical Treatment of Amenorrhea - Galactorrhea
Syndromes with Vitamin B6 (Pyridoxine)

Investigators:

Principal: Robert A. Vigersky, MD, MAJ, MC
Gerald S. Kidd, MD, MAJ, MC

Objectives:

To evaluate the effects of pyridoxine on the elevated levels of prolactin and on the symptoms of amenorrhea and galactorrhea.

Technical Approach: Pre- and post-treatment testing of LH, FSH, Prolactin, growth hormone and TSH with TRH, LRH and intravenous pyridoxine tests.

Progress & Results: 6 patients have been studied with results being presently analyzed. Preliminary review shown no effect of acute or chronic B6 treatment on Prolactin, amenorrhea or galactorrhea.

Conclusions: B6 does not improve symptoms or prolactin in patients with amenorrhea - galactorrhea syndromes.

Funds Utilized FY-78: 2600 Consumable supplies

Funding Requirement FY-79:

Personnel	1100
Supplies	750
Non-expendable; loose issue	
Printing, publication	250
Rental	100
Contractual Svcs.	3500
Isotopes	
Equipment	
Travel	500
TOTAL	<hr/> \$6,200

Publications: None.

Type of report: Interim.

Work Unit No.: 1363

Title of Project: Effect of T3 and rT3 on Plasma Cyclic Nucleotide Levels on Sheep.

Investigators:

Principal: H. Linton Wray, LTC, MC

Associates: Kenneth D. Burman, MAJ, MC
John P. Alford, CPT, V.C.,
Leonard Wartofsky, LTC, MC

Objective: To determine if plasma levels of cyclic AMP and cyclic GMP are changed by administration of 3,5,3'triiodothyronine and 3,3',5'triiodothyronine (reverse T3, rT3).

Technical Approach: Plasma cyclic AMP, cyclic GMP and serum T3, rT3 and T4 will be measured before, during and after 6 days of intramuscular administration of placebo, T3, rT3 or both T3 and rT3 together. Six animals will comprise each treatment group. The 12 day study period consists of 3 days of baseline, 6 days of treatment with thyronine given every 8 hours and 3 days of recovery. Morning blood samples will be obtained on days 1-5 and 8-12. The first dose of each hormone will be given intravenously and blood collections made at 0, 60, and 180 minutes. Blood samples will be obtained 7 hours after the morning treatment on day 8. Pretreatment thyroid stimulating hormone (TSH) levels will be determined on days 1-3 in each 12 day study period. After the last dose of each hormone at 0700 on day 9, a thyrotropin releasing hormone (TRH) test will be performed with an intravenous bolus injection of 400 ug of TRH and blood collections at -30, 0, 30, 60, 90, and 120 minutes for TSH.

Progress & Results: Five groups of sheep have completed the study protocol with the following treatments (1) placebo, (2) 1.5 ug T3/kg body weight, (3) 4.5 ug T3/kg body weight, (4) 4 ug rT3/kg body weight, and (5) 1.5 ug T3/kg body weight and 2.5 ug rT3/kg body weight. Measurement of the experimental parameters is only partially completed. Analysis of the cyclic nucleotide data revealed that only the high dose of T3 changed the cyclic nucleotide levels. Lower dose of T3 only or in combination with rT3 did not change even cyclic nucleotide levels. T3 of 4.5 ug/kg caused a 52% increase in cyclic AMP without changing cyclic GMP. Measurements of the serum levels of T3 and rT3 metabolites, 3,3'-diiodothyronine (3,3'T2), 3',5'-diiodothyronine (3',5'T2) and 3'-monoiodothyronine (3'T1) has been performed on the samples from there study. Administration of T3 at both doses increased 3,3'T2 without increasing 3',5'T2 or 3'T1. Administration of rT3 alone or in combination with T3 increased 3,3'T2 and 3',5'T2 with only a minimal and non-statistically significant increase in 3'T1.

Conclusions: Short-term elevations of serum T3 and rT3 to levels associated with hyperthyroidism caused no change in plasma cyclic AMP or cyclic GMP. Higher levels of T3 caused an increase in cyclic AMP without changing cyclic GMP. The increases noted in the thyronine metabolites suggest that; 1) T3 and rT3 are important precursors of 3,3'T2, 2) rT3 is an important precursor of 3',5'T2, 3) T3 may cause increased conversion of rT3 to 3,3'T2 and 3',5'T2 and 4) 3'T1 is present in normal sheep serum and not changed significantly by short-term increases in its putative precursors, 3,3'T2 and 3',5'T2.

Funds Utilized, FY-78:

2600	Consumable supplies	5,400
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Funds Requested, FY-79:

1100	Personnel	3,050
2600	Exp. Supplies	3,500
2400	Reprints, printing	500
	Audiovisual	-
2319	Xerox, office supplies	200
	Isotopes	-
2572	Lab Contracts	-
3100	Loose issue, non-exp.	-
	Animals	-
2100	Travel	600
	Equipment	-

TOTAL		<u>\$7,800</u>
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Publications:

Wray, H.L., Burman, K.D., Alford, J.P., and Wartofsky, L., Effect of T3 and Reverse T3 (rT3) Administration on Plasma Cyclic AMP (CAMP) and Cyclic GMP (CGMP) in Sheep, Clin. Res. 26: 16A, 1978.

Wray, H.L., Burman, K.D., Smallridge, R.C., Alford, J.P., and Wartofsky, L., Effect of T3 and Reverse T3 (rT3) Administration on Serum Tri-, Di-, and Mono-Iodothyronines in Sheep, Fed. Proc. 37, 519, 1978. Presented in Atlantic City, April, 1978.

Type of report: Interim.

Work Unit Number: 1364

Title of Project: Effect of L-tryptophan on LH and FSH dynamics in women

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if administration of the amino acid L-tryptophan can alter the dynamics of reproductive hormones in women.

Technical Approach: Basal hormone levels, response to LHRH, and response to estradiol benzoate will be determined during two menstrual cycles: one control, and one during which L-tryptophan is given.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

No subjects have yet been studied because of difficulty in recruiting subjects and lack of time of available medical personnel. Approval from Clinical Investigation committee to pay volunteers to facilitate this study has been obtained. Arrangements for measurement of the appropriate hormones have been completed. It is anticipated that recruitment of all volunteers and collection of all studies can be completed during FY 79.

Funds Utilized, FY-78: 2500 Consumable supplies \$93.29

Funding Requirement, FY-79:

Personnel	1,500
Travel	400
Rental	200
Printing & Reproduction	100
Contractual Svcs.	4,000
Supplies	3,500
Non-expendable equipment	
TOTAL	<hr/> \$9,700

Work Unit Number: 1365

Title of Project: Insulin Resistance in Diabetes: Relative Effect on Glucose and Amino Acids

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine whether, in states associated with impedance to the action of insulin, this impedance affects glucose and amino acid disposal equally.

Technical Approach: Measurement of rate of disappearance of bolus loads of glucose and valine in subjects with diseases associated with insulin impedance.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

The necessary prerequisite for this study, development of an assay for the rapid measurement of valine in serum, has been completed by Lt Bongiovanni, and a paper has been accepted for publication. Studies on the preparation of the valine for administration to humans have almost been completed. No subjects have yet been studied as certain critical equipment is temporarily out of federal stock. If this equipment becomes available in a timely fashion, it is anticipated that most of the subject recruitment and the actual studies will be completed during FY 79.

Funds Utilized, FY-78: 2600 Consumable supplies \$7,701.79

Funding Requirement, FY-79:

Personnel	2,500
Travel	600
Rental	200
Printing & Reproduction	200
Contractural Svcs.	300
Supplies	4,500
Non-expendable equipment	

TOTAL	\$8,300
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Work Unit No.: 1366

Title of Project: The effect of glucagon and thyroid economy.

Investigators:

Principal: Kenneth D. Burman

Objective: To determine if glucagon administration influences thyroid hormone levels.

Technical Approach: Glucagon infusions are administered to fed and fasting patients, and changes in T3 and rT3 are noted.

Progress & Results: 20 patients have been studied, and glucagon administration did not change T3 and rT3 levels.

Conclusions: None.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Persennel	2,000
Travel	
Rental	
Printing & Reproduction	400
Contractual Svcs.	2,000
Consumable supplies	2,000
Non-expendable equipment	
MEDCASE	
TOTAL	<u>\$6,400</u>

Publications: In preparation.

Type of report: Interim.

Work Unit Number: 1367

Title of Project: Effect of methyldopa on serum LH and testosterone in hypertensive men

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if methyldopa and clonidine, which are thought to exert central effects on neurotransmitters, can alter the function of the hypothalamic-pituitary-testicular axis.

Technical Approach: Measurement of basal hormone levels and performance of HCG tests in hypertensive men before and after they are started on methyldopa or clonidine.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Great difficulty has been encountered in recruiting subjects, and no patient has yet been studied under this protocol. Preliminary work is continuing. The possibility of doing this study in collaboration with personnel at other centers where recruitment would be easier is being considered.

Funds Utilized, FY-78: 2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	4,000
Travel	400
Rental	200
Printing & Reproduction	100
Contractural svcs.	4,000
Supplies	3,500
Non-expendable equipment	
TOTAL	<hr/> \$12,200

Work Unit No.: 1368

Title of Project: Effect of Dietary Phosphate on Serum Levels
of Vitamin D Metabolites in Hypoparathyroidism.

Investigators:

Principal: H. Linton Wray, LTC, MC

Associate: Marcus Schaaf, MD, Joseph Bruton, Ph.D

Objective: To determine if serum levels of 25-OH-D (25-hydroxy-vitamin D), 24, 25-(OH)₂-D (24,25-dihydroxyvitamin D) and 1,25 - (OH)₂ - D (1, 25-dihydroxyvitamin D) are changed by short-term manipulation of dietary phosphate intake in hypoparathyroid patients.

Technical Approach: Eight hypoparathyroid patients will be studied during changes in phosphate intake to determine the effect on serum levels of 25-OH-D, 24, 25-(OH)₂-D and 1, 25-(OH)₂-D. The 15 day protocol consists of 2 days on normal phosphate intake (1.0 g of phosphorus), 10 days on low phosphate intake (0.5 g of phosphorus) and 3 days on high phosphate intake (1.5 g of phosphorus). During the period of phosphate restriction, phosphate-binding antacids will be given (aluminum hydroxide gel with magnesium hydroxide (Maalox), 60 ml at 0800, 1200, 1500 and 2000 and aluminum hydroxide gel suspension (Amphojel), 30 ml at 1000, 1400, 1800, and 2200). During the period of phosphate excess, supplemental sodium-potassium phosphate will be given (1.0 g of phosphorus per day, (Neutro-Phos solution), 100 ml at 0900, 1400 and 1700). Adjustments will be made in the dosage of antacids and phosphate supplements as necessary to prevent either constipation or diarrhea. Caloric and calcium intakes as well as all medications including Vitamin D will remain constant throughout the study. Twenty-four urine collections will be made daily for determination of inorganic phosphate, calcium, magnesium and creatinine. A 45 ml blood specimen will be obtained approximately every other day for a total of 9 blood collections. Serum inorganic phosphate, ionized calcium, total calcium, magnesium and creatinine and plasma 25-OH-D, 24, 25-(OH)₂-D and 1, 25-(OH)₂-D will be determined. A 10 ml blood specimen for serum PTH will be collected on the last day of each of the three study periods.

Progress & Results: Four patients have undergone this protocol which was effective in regard to lowering the urinary and serum phosphate levels. The assays for the Vitamin D metabolites have not been adequately worked out and, therefore, delay the critical analyses for this study. The methodologies of these assays is presently undergoing modification and should be usable in the near future.

Conclusions: None.

Funds Utilized FY-78:

2600

Supplies

13,200

Funds Requested FY-79:

1100	Personnel	10,050
2600	Supplies	11,300
2400	Reprints	500
	Audiovisual	-
2319	Xerox, Misc.	200
	Isotopes	-
2572	Contracts	3,600
	Consultants	-
	Loose issue	-
3100	Non-exp. Supplies	-
	Animals	-
2100	Travel	800
	Equipment	-
	Medcase	5,000

TOTAL

\$31,450

Publications: None.

Type of report: Interim.

Work Unit No.: 1369

Title of Project: A Prospective Study of the Effects of
Propranolol on Hypercalcemia in Hyperthyroidism
and Hyperparathyroidism.

Investigators:

Principal: H. Linton Wray, LTC, MC

Associates: Gerald S. Kidd, MAJ, MC
Kenneth D. Burman, MAJ, MC
Leonard Wartofsky, LTC, MC

Objective: To determine if propranolol is an effective treatment for the hypercalcemia of either hyperthyroidism or hyperparathyroidism.

Technical Approach: Hypercalcemic patients with hyperparathyroidism and hyperthyroidism will be studied as inpatient to determine the effect of a seven-day course of propranolol on their bone mineral metabolism. After an equilibration period and while on a constant diet, serum ionized and total calcium, phosphate, total protein, albumin, alkaline phosphatase, parathyroid hormone, calcitonin, and creatinine and urinary cyclic AMP will be determined during a control periods, during and after treatment.

Progress & Results: This protocol has had a slow start because of the limited number of suitable patients so far identified. An increased effort should locate more patients in the future.

Conclusions: None.

Funds Utilized in FY-78:

2600	Consumable Supplies	200
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Funds Requested FY-79:

1100	Personnel	3,550
2100	Travel	400
2319	Rental	200
2400	Printing	100
2572	Contract Svc.	3,000
2600	Consum. Supp.	2,500
3100	Non-Expen. Equip	-
	Medcase	2,000

TOTAL	11,750
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Publications: None.

Type of report: Interim.

Work Unit No.: 1370

Title of Project: Sex Steroid Receptors in the Human Thyroid Gland.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC

Objectives: To detect, quantitate and characterize the estrogen receptor in the human thyroid gland.

Technical Approach: Thyroid tissue, obtained at the time of surgery, will be homogenized in Tris-EDTA-DTT buffer. The tissue homogenate will be centrifuged at 100,000 x g and the cytosol incubated with high specific activity tritiated estradiol in varying concentrations with and without 100 fold excess of cold estradiol. A Scatchard plot will be constructed from the data which yields the affinity constant and maximum binding capacity.

Progress & Results: Tissue is being accumulated but the technique is still being worked out using rat thyroid tissue.

Conclusions: None.

Funds Utilized, FY-78:

2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	1,100
Supplies, general	
Non-expendable; loose issue	
Printing, publication	100
Rental	200
Animals	
Isotopes	
Equipment	
Travel	

TOTAL	<hr/> \$1,400
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Publications: None.

Type of report: Interim.

Work Unit No.: 1371

Title of Project: Glucose regulation, Peripheral Thyroid Hormone Economy, in fasted subjects.

Investigators:

Principal: Kenneth D. Burman

Objective: To determine if glucose administration during fasting alters thyroid hormone levels.

Technical Approach: Glucose administration for 600 calories a day is administered to fasting patients, and T3 and rT3 levels measured.

Progress & Results: Thyroid hormone levels change depends on the carbohydrate content of the diet. Diet influences thyroid hormone levels.

Conclusions: None

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	2,000
Travel	500
Rental	200
Printing & Reproduction	400
Contractual Svcs.	500
Consumable Supplies	5,500
Non-expendable equipment	
MEDCASE	1,000
TOTAL	<u>\$10,100</u>

Publications: Burman K.D., O'brian, Paper submitted to Metabolism.

Type of report: Interim

Work Unit No.: 1372

Title of Project: Alterations in TSH response to TRH in obesity and fasting.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if TSH response to TRH changes in fasting .

Technical Approach: Patients are admitted to the hospital and TRH test administered during fed and fasting states, and the results compared.

Progress & Results: It has been conclusively determined that the TSH response to TRH diminished during fasting.

Conclusions: Thyroid hormone levels change during fasting.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	2,000
Travel	500
Rental	200
Printing & Reproduction	400
Contractual Svcs.	2,000
Consumable supplies	6,000
Non-expendable equipment	
MEDCASE	2,000
TOTAL	<u>\$13,100</u>

Publications: Paper submitted to Metabolism.

Type of report: Interim.

Work Unit No.: 1373

Title of Project: The Effect of Protein Ingestion on Thyroid Hormone Economy.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if protein influences thyroid hormone levels.

Technical Approach: Patient's are admitted to the hospital and fasted, and then refed various amounts of protein from 200-800 calories and is determined whether protein levels influence T3 levels.

Progress & Results: Protein is not as efficacious as carbohydrate in influencing serum T3 and rT3 levels.

Conclusions: Diet influences thyroid hormone levels.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	2,000
Travel	500
Rental	200
Printing & Reproduction	400
Contractual Svcs.	2,500
Consumable supplies	5,000
non-expendable equipment	
MEDCASE	1,000
TOTAL	<u>\$11,600</u>

Publications: K.D. Burman, Jack O'Brian, Paper presented in Boston, AFRCR meeting, February 1978, and October 1978.

Type of report: Interim

Work Unit Number: 1374

Title of Project: Evaluation of testosterone reserve in infertile men

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if idiopathic oligospermia may be associated with defective Leydig cell function.

Technical Approach: Performance of HCG tests and measurement of testosterone production rate in infertile men.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Approximately 35 subjects have had HCG tests under this protocol. Initial results show that the acute testosterone response to HCG (2 hrs) correlates well with the response to the standard (4 day) test, thus enabling the development of a suitable outpatient screening test. A paper detailing this finding has been submitted for publication. Measurements of 17-OH-progesterone and estradiol on some of the subjects have been completed, and an addendum to permit the use of Pergonal along with HCG has been approved. Work on the development of the methods for testosterone production rate is intensively going on. It is anticipated that this protocol will be extremely actively pursued during FY 79. Progress has been somewhat slowed by delays in obtaining the temporary hire technician approved to work on this study.

Funds Utilized, FY-78:

2600 Consumable supplies \$3,408.10

Funds Required, FY-79:

Personnel	4,000
Travel	600
Rental	200
Printing & Reproduction	200
Contract Svcs.	500
Supplies	6,000
Non-expendable equipment	
	..
TOTAL	<u>\$11,500</u>

Work Unit Number: 1375

Title of Project: Effect of separating protein from carbohydrate in the dietary treatment of diabetes

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine the optimum diet for diabetics by seeing if separation of protein from carbohydrate will reduce hyperglycemia

Technical Approach: Measurement of blood sugar and urinary sugar in diabetics on two occasions: a standard diet, and a modified diet in which most of the daily protein is given in a meal containing little carbohydrate

Type of Report: Terminated

Progress, Results, Conclusions, and Publications:

Because of the pressure for beds on the metabolic ward and the lack of time of the investigators involved, no subjects could be studied under this protocol in FY 78. Preliminary work, including development of hemoglobin A1C assay, is ongoing.

Funds Utilized, FY-78: 2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	1,000
Travel	
Rental	200
Printing & Reproduction	100
Contract svcs.	100
supplies	1,000
Non-expendable equipment	

TOTAL	<hr/> \$2,400
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Work Unit Number: 1376

Title of Project: Effect of amitriptyline and amantadine on growth hormone dynamics in acromegaly.

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if either amitriptyline or amantadine might be a suitable medical treatment for patients with acromegaly, and what their mechanism of action is.

Technical Approach: Measurement of serum growth hormone levels in acromegalic patients before and after a one month course of amitriptyline or amantadine.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Several phases of this project have been partially completed. 5 subjects were given amitriptyline, and 3 appeared to have reduced their growth hormone output. A paper detailing this finding has been submitted for publication. As a byproduct of this study, it was found, that, in contrast with normal subjects, patients with acromegaly do not show an increase in serum growth hormone after L-tryptophan, and a paper detailing this finding has been submitted. Recruitment is currently ongoing for the amantadine phase of the study and, based on the results described above, additions to this protocol in the same general area are now being prepared.

Funds Utilized, FY-78:

2600 Consumable supplies \$8,473.00

Funding Requirement, FY-79:

Personnel	3,000
Travel	600
Rental	200
Contracts scs.	300
Printing	300
Supplies	2,000
Non-expendable equipment	

TOTAL

\$6,400

Work Unit Number: 1377

Title of Project: Effect of dietary tryptophan content on food intake in obese subjects

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if the ratio of certain amino acids in the diet will determine food intake in humans.

Technical Approach: Measurement of food intake in obese subjects on liquid diets containing different proportions of essential amino acids.

Type of Report: Terminated

Progress, Results, Conclusions, and Publications:

Because of limited space on the metabolic ward and lack of time of the medical personnel involved, no subjects were studied under this protocol in FY 78. Preliminary work on the development of the appropriate liquid diets and improving the palatability is ongoing.

Funds Utilized, FY-78:

2600 Consumable supplies 20.00

Funding Requirement, FY-79:

Personnel	1,000
Travel	
Rental	200
Printing	100
Contracts svcs.	100
supplies	1,000
Non-expendable equipment	

TOTAL

\$2,400

Work Unit Number: 1378

Title of Project: Effect of four-hour ACTH infusion on plasma steroids

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine the response of plasma steroids to 4 hour ACTH infusion in various disease states.

Technical Approach: Performance of standard 4 hour ACTH infusion in various disease states.

Type of Report: Terminated

Progress, Results, Conclusions, and Publications:

A pilot study was done on this project and the results were promising, indicating a fall in serum testosterone after ACTH. Work on the development of the plasma steroid assays is ongoing. However, several recent publications have appeared on this topic, and this protocol is currently undergoing a re-examination with a view toward modification to prevent duplication of work done by others.

Funds Utilized, FY-78:

2600 Consumable supplies 797.29

Funding Requirement, FY-79:

Personnel	1,000
Travel	
Rental	200
Printing	100
Contracts	100
Supplies	1,000
Non-expendable equipment	
TOTAL	<hr/> \$2,400

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Work Unit Number: 1379

Title of Project: Effect of post-weaning undernutrition on reproductive hormones in rats

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine how undernutrition early in an animal's life affects endocrine function and sexual maturation.

Technical Approach: Determination of hormonal dynamics in animals fed different diets.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Several experiments have been completed under this protocol. One showed that thyroid function appeared to depend on the composition of the diet fed, and a paper detailing this finding has been accepted for publication. A second paper detailing how undernutrition affects the reproductive hormonal development has also been accepted for publication. Additional experiments are currently underway to explore the possibility that undernourished animals have overproduction of "inhibin", the specific substance which specifically inhibits output of FSH from the pituitary. Elucidation of the role of inhibin is currently a very active area in endocrinology.

Funds Utilized, FY-78: 2600 Consumable supplies \$183.75

Funding Requirement, FY-79:

Personnel	2,000
Travel	600
Rental	200
Printing	300
Contracts	300
Supplies	3,500
Non-expendable equipment	
TOTAL	<hr/> \$6,900

Work Unit No.: 1380

Title of Project: Effect of Thyroid Status on the Hormonally-induced Cyclic AMP Responses of the Kidney.

Investigators:

Principal: H. Linton Wray, M.D., LTC, MC

Associate: Gerald S. Kidd, M.D., MAJ, MC

Objective: To determine if the renal hormone receptor - second messenger systems of two unrelated polypeptide hormones are affected by thyroid hormone. By measuring nephrogenous cyclic AMP during parathyroid and antidiuretic hormone infusions in hyper- and hypothyroid patients, it can be determined if thyroid hormone influences the renal cyclic AMP responses to these hormones.

Technical Approach: Six patients with hyperthyroidism and six hypothyroidism will be admitted to Ward 30 for a 3 day study protocol and will be similarly studied 2 months after becoming euthyroid. During each admission the patient will undergo two 3-hour renal clearance procedures, one with PTH infusion and another with vasopressin infusion. Parathyroid hormone infusion will be given as 50 units IV push in 25ml of D₅W and 150 units in 75ml of D₅W over one hour. Urine will be collected for calcium, phosphate, creatinine and cyclic AMP measurements and blood for ionized calcium, total calcium, creatinine, phosphate and cyclic AMP. The vasopressin infusion will be given similarly with 0.2 units IV push and 0.6 units over one hour. Osmolarity, creatinine and cyclic AMP will be measured in blood and urine.

Progress and Results: Six hyperthyroid and four hypothyroid patients as well as three euthyroid patients taking thyroxine have been studied. The hypothyroid patients had a reduced excretion of an oral H₂O load, a low basal ionized calcium, high parathyroid hormone and nephrogenous cyclic AMP. The hyperthyroid patients appeared normal except for a low fractional excretion of phosphate. The responses to parathyroid hormone and vasopressin in these two groups differed only in that the hyperthyroid patients had a greater increase in plasma cyclic AMP after parathyroid hormone.

Conclusions: The delayed water excretion in hypothyroid patients and the decreased fractional excretion of phosphate in hyperthyroid patients are not associated with demonstrable changes in renal responses to vasopressin and parathyroid hormone; therefore, thyroid status has small if any effect on the hormone receptor-second systems of cyclic AMP studied in this investigation.

Funds Utilized, FY-78:

2600	Supplies	\$4,500
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Funding Requirement, FY-79:

Personnel	5,700
Travel	400
Rental	200
Printing & Reproduction	150
Contractual Svcs.	4,200
Consumable supplies	3,800
Non-expendable equipment	
MEDCASE	4,000
TOTAL	<u>\$18,450</u>

Publications:

Kidd, G.S., and Wray, H.L., Effect of Thyroid Status on Renal Responses to Parathyroid Extract (PTE) and Vasopressin (VP), Endocrinology, 102 (Suppl.): 479, 1978.

Type of report: Interim.

Work Unit No.: 1381

Title of Project: Estradiol (E2) Receptors in Rat Thyroid Glands.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC
Joseph Bruton, Ph. D.

Objectives: To detect, quantitate and physico-chemically characterize the receptor for estradiol in rat thyroid tissue.

Technical Approach: Twenty-five rats are sacrificed for each experiment and their thyroid tissue is pooled. Rats are previously gonadectomized with some being treated with exogenous estrogen or androgen. A 100,000 x g cytosol is prepared from the thyroid homogenate and the cytosol is evaluated by binding parameters, sucrose density gradient centrifugation and gel filtration for size and charge characteristics and varying other steroids for relative binding affinities.

Progress & Results: An estradiol receptor has been found to be present in rat thyroid cytosol which is greater in females than males and whose concentration can be varied depending on the gonadal status of the animals.

Conclusions: An E2 receptor has been found for the first time in thyroid tissue.

Funds Utilized FY-78:

2600	Consumable supplies	\$4,928.05
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Funding Requirement, FY-79:

Personnel	10,200
Supplies, general	8,600
Non-expendable; loose issue	
Printing, publication	200
Rental	200
Contractural Svcs.	100
Equipment	
Travel	500
TOTAL	<u>\$19,800</u>

Publications: None

Type or report: Interim

Work Unit No.: 1382

Title of Project: Measurement of Steroids in Fluid Obtained by Micropuncture from Rat Seminiferous Tubules and Epididymis.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC

Objectives: To quantitate the levels of estradiol, testosterone and dihydrotestosterone intra-tubularly in order to help understand the regulation of spermatogenesis.

Technical Approach: Rats are anesthetized and their testes exposed through a scrotal incision. Using micropipettes made in the laboratory, tubules are punctured and small volumes of fluid withdrawn. Sperm is separated from seminal fluid by centrifugation. Micro-assays will measure the quantity of steroids in the fluid.

Progress & Results: Over the past year, over 100 microliters of fluid has been obtained on steroid. Micro-assays for the steroids are currently being developed.

Conclusions: None.

Funds Utilized FY-78:

2600 Consumable supplies \$5,672.66

Funding Requirement FY-79:

Personnel	16,500
Supplies, general	1,900
Non-expendable; loose issue	
Printing, publication	250
Rental	200
Contractual Svcs.	100
Isotopes	
Equipment	
Travel	400
TOTAL	<u>\$19,350</u>

Publications: None.

Type of report: Interim.

Work Unit No: 1383

Title of Project: Measurement of Hemoglobin A-1-C in the Assessment of the Efficacy of Diabetic Treatment.

Investigator: Timothy M. Boehm, MAJ MC

Objectives:

a) To compare hemoglobin A-1-C measurements with more established indicators of diabetic control -- namely fasting and postprandial glucoses, outpatient single voided urines, and 24 hour urinary glucose.

b) To evaluate the response of hemoglobin A-1-C to modifications of diabetic therapy.

c) To attempt to match diabetics presenting with nephropathy and retinopathy with similar diabetics without complications regarding age, sex, duration of disease, and insulin requirement and to compare hemoglobin A-1-C concentrations in the groups with and without diabetic complications.

d) 1) To establish a valid Hgb A-1-C assay.

2) To evaluate hemoglobin A-1-C to effective and ineffective diet therapy of diabetes.

e) An automated HPLC method for measuring hgb A-1-C has been established.

f) Interassay and intraassay variation have been quantitated and are acceptable. The normal range for high A-1-C is 6.7 ± 1.2 , and many diabetics have high values for hgb A-1-C. The current emphasis is at attempting to correlate decreases in hgb A-1-C with successful weight reduction in adult onset diabetes.

Conclusions: None at present

Funds Utilized, FY-78: \$2,800 for supplies, reagents

Funds Requested, FY-79: \$3,360 for supplies, reagents

Publications: A manuscript describing an automated HPLC method for hgb A-1-C is in preparation. It is hoped that an abstract will be submitted for the American Diabetes Association meeting in June 1979.

Type of report: Interim

Work Unit No.: 1384

Title of Project: The Effect of Isoniazide (INH) on Prolactin, Gonadal Function, and Pyridoxine (B6) Metabolism.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC
Gerald S. Kidd, MAJ, MC

Objectives: To evaluate whether or not INH-induced pyridoxine deficiency elevates plasma prolactin levels and/or affects gonadal function in adult men and women.

Technical Approach: 10 men and 10 women who will receive INH for PPD conversion will receive formal evaluation of their Prolactin and Gonadal status before and at 3 and 6 months after being placed on INH. Plasma pyridoxal phosphate and kinase activity will also be measured.

Progress & Results: This project will be begun by Dr. Kidd in El Paso, TX as soon as revision of the Patient Information Sheet is approved. KMU will support his activity by measurement of steroids, prolactin and gonadotropin as previously planned.

Conclusions: None.

Funds Utilized, FY-78: 2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	2,400
Supplies, general	1,300
Non-exp.; loose issue	
Printing, publication	100
Rental	200
Animals	
Contracts	1,750
Equipment	
Travel	500

TOTAL	\$6,250
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Publications: None.

Type of report: Interim,

Work Unit Number: 1385

Title of Project: Serial changes in free testosterone during pregnancy: correlation with HCG levels and fetal sex

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if measurement of free testosterone in maternal blood is predictive of fetal sex.

Technical Approach: Measurement of serial free testosterone in pregnant women and correlation with gestational age and ultimate sex of offspring.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Liaison between endocrine and obstetric service to recruit patients has been established, and methodology for free testosterone assay is being validated. Patient recruitment will begin as soon as final logistic arrangements are made.

Funds Utilized, FY-78: 2600 Consumable supplies \$83.75

Funding Requirement, FY-79:

Personnel	2,500
Rental	200
Travel	400
Printing	100
Contracts	2,000
Supplies	3,000
Equipment	

TOTAL	<hr/> \$8,200
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Work Unit No.: 1386

Title of Project: The Effect of Δ^1 -Testolactone (Teslac) in Male Infertility.

Investigators:

Principal: Robert A. Vigersky, MD, MAJ, MC

Objectives: To increase sperm counts in infertile men with oligospermia by lowering plasma estradiol levels.

Technical Approach: 10 men will be given Teslac for 6-12 months with evaluation of seminiferous tubular and Leydig cell function before and at the end of treatment. Pre-treatment evaluation also includes testicular biopsy with routine histologic examination and immunofluorescent studies.

Progress & Results: 4 men have been started on treatment. There appears to be a favorable response in 4 men so far.

Conclusions: Teslac may increase sperm counts in oligospermic men.

Funds Utilized, FY-78: 2600 Consumable supplies \$12,993.83

Funding Requirement FY-79:

Personnel	11,523
Supplies, general	12,500
Non-expendable; loose issue	
Printing, publication	250
Rental	300
Animals	
Contractual Svcs.	2,750
Equipment	
Travel	400
TOTAL	<u>\$27,723</u>

Publications: None.

Type of report: Interim.

Work Unit Number: 1387

Title of Project: Acute responses to estrogen in men with prostate carcinoma

Principal Investigator: Allan R. Glass, M.D., MAJ MC

Objectives: To determine if chronic estrogen treatment of men with prostate carcinoma alters the way their hormones respond to the estrogen.

Technical Approach: Measurement of response to acute estrogen injection in men with prostate cancer before and after chronic estrogen therapy.

Type of Report: interim

Progress, Results, Conclusions, and Publications:

Liaison with urology service has been established and patient recruitment is underway. Logistic procedures for obtaining appropriate blood specimens are being evolved.

Funds Utilized, FY-78: 2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	3,000
Travel	400
Rental	200
Printing	100
Contracts	2,000
Supplies	4,500
Equipment	

TOTAL	<u>\$10,200</u>
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Work Unit No.: 1388

Title of Project: The developement of a radioimmunoassay for T0, and 3,5'T2.

Investigator:

Principal: Keith R. Latham
Kenneth D. Burman

Objective: To obtain immunoassays for thyronine, and 3,3'T2.

Technical Approach: Antibodies are generated and tags made by labeling I-125 artritium and serum samples are tested.

Progress & Results: We have presently made antibodies for both T0, 3,5'T2. Making the radiolabel for 3,5'T2 has been difficult. It has recently been accomplished and it is hoped that serum levels will be determined in the near future.

Conclusions: None.

Funds Utilized, FY-78: \$ 16,735.27

Funding Requirement, FY-79:

Personnel	2,000
Travel	400
Rental	200
Printing & Reproduction	300
Contractual Svcs.	300
Consumable supplies	5,000
Non-expendable equipment	1,000
MEDCASE	
TOTAL	<hr/> \$9,700

Publications: None

Type of report: Interim.

Work Unit No.: 1389

Title of Project: The Effect of Dietary Carbohydrate on T3 Receptors.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if diet influences T3 receptors.

Technical Approach: Various diets contain various amounts of carbohydrate are administered to rats, and their receptors localized, and their receptor number determined.

Progress & Results: It has been determined that the amount of carbohydrate in the diet, the more the number of receptors.

Conclusions: Carbohydrate influences the number of receptors.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	
Travel	
Rental	
Printing & Reproduction	
Contractual Svcs.	2,500
Consumable supplies	6,000
Non-expendable equipment	
MEDCASE	

TOTAL	<hr/> \$8,500
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Publications: None.

Type of report: Interim

Work Unit No.: 1390

Title of Project: Investigation concerning the physiology of iodothyronines during fasting.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if the thyroid hormone levels and kinetics change during fasting.

Technical Approach: Patients are fasted and kinetics are determined before and during the fast.

Progress & Results: It has been determined that various changes occur during fasting, specifically that reverse T3, and 3'5' levels increase, probably due to delay in clearance rates.

Conclusions: Thyroid hormone levels change during fasting.

Funds Utilized, FY-78:

Funding Requirement, FY-79:

Personnel	
Travel	
Rental	
Printing & Reproduction	
Contractual Svcs.	4,000
Consumable supplies	3,000
Non-expendable equipment	
MEDCASE	
TOTAL	<u>\$7,000</u>

Publications: None.

Type of report: Interim.

Work Unit No.: 1391

Title of Project: Regulation of the initiation of thyroid hormone action.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine the mechanism by which thyroid hormones act.

Technical Approach: Isolated nuclei are solubilized nuclei are determined by use or addition of sulfhydryl agents whether the receptor number increases or decreases is determined.

Progress & Results: Sulfhydryl groups definitely are required for a binding of T3 to its receptor.

Conclusions: The receptor is dependent on sulfhydryl groups.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	
Travel	
Rental	
Printing & Reproduction	
Contractual Svcs.	4,000
Consumable supplies	3,500
Non-expendable equipment	
MEDCASE	
TOTAL	<u>\$7,500</u>

Publications: None.

Type of report: Interim

Work Unit No.: 1392

Title of Project: Steroid Transfer Across the Blood-Cerebrospinal Fluid Barrier in the Rhesus Monkey.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC
Joseph Bruton, Ph.D.

Objectives: To evaluate the kinetics of steroid entry and exit in the cerebrospinal fluid and the effect of cancer chemotherapeutic agents on these kinetics.

Technical Approach: Rhesus monkeys with indwelling ventricular catheters are injected higher intravenously or intra-theccally with hydrocortisone, prednisone or dexamethasone in varying doses with and without the inclusion of methotrexate and/or cytosine arabinoside.

Progress & Results: The entry time of steroids into the CSF appears to be independent of dose or type of steroid. The maximum concentration is dose dependent. No effect of chemotherapeutic agents on steroid kinetics has been found or vice versa.

Conclusions: Steroids rapidly enter and exit the CSF but none of the steroids tested appeared to be more advantageous in this respect. Chemotherapy does not affect steroid CSF kinetics.

Funds Utilized FY-78: \$542.00

Funding Requirement FY-79:

Personnel	1,100
Supplies, general	1,750
Non-expendable; loose issue	
Printing, publication	100
Rental	200
Contracts	200
Isotopes	
Equipment	
Travel	400
TOTAL	\$3,750

Publications: Gangji, D., Vigersky, R., Cohen, L., Glaubiger, D., Bruton, J., and Poplack, D., "Pharmacokinetics of Corticosteroids in Cerebrospinal Fluid (CSF) and Blood", Clin. Res. 26: 289A, 1978.

Gangji, D., Vigersky, R., Bleyer, A., Glaubiger, D., and Poplack, D., "Corticosteroid Kinetics in CSF", in Kay, H., and Whitehouse, M., eds. CNS Complications of Malignant Disease, McMillan Press, Ltd., London, 1978, in press.

Type of report: Interim.

Work Unit No.: 1393

Title of Project: T3 Receptors in Normal and Fasting Rats.

Investigator:

Principal: Kenneth D. Burman

Objective: To determine if T3 receptor number changes in fed and fasting rats.

Technical Approach: Rats are fasted for 72 hours and compared, and scatchard plots made of their hepatic nuclei when isolated. T3 receptors are determined by classic scatchard plots.

Progress & : Number of receptors in rats that are fasting, decreases.

Conclusions: Various states such as fasting can alter T3 receptor number.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	1,000
Travel	
Rental	
Printing & Reproduction	400
Contractual Svcs.	
Consumable supplies	300
Non-expendable equipment	
MEDCASE	

TOTAL	<u>\$1,700</u>
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Publications: K.D. Burman, et al, Endocrinology, October 1977.

Type of report: Interim.

Work Unit No.: #1394

Title of Project: The Development of a Radioimmunoassay of
Triiodothyronine.

Investigators:

Principal: Kenneth D. Burman

Objective:

To develop immunoassays for various iodothyronines. For 12 hour specific
characterization of the enzymes involved in T3 to T4 conversion.

Pogress & Results:

Assays could develop far various iodothyronines including T4 , T3, 3,5T2,
3'5'T2, 3'T1, 3,3'T2. Use of these assays has allowed specific
characterization of the enzymes involved in conversion in the liver.

Funds Utilized FY-78:

\$500

Funds Requested FY-79:

\$1,000

Publications:

Type of report: Interim.

Work Unit No.: #1395

Title of Project: T4 to T3 Conversion: Effect of Modulation of Glucose Metabolism.

Investigators:

Principal: Kenneth D. Burman, MAJ, MC

Associates:

Objectives: The objectives of this study are to effect of glucose on T4 to T3 conversion and T3 receptors.

Progress & Results: To date no studies have been performed in this protocol.

Funds Utilized FY-78:

None

Funds Requested FY-79:

Approximately

\$2,000.00

Work Unit No.: #1396

Title of Project: T4 to T3 Conversion: Effect of Somatostatin Administration.

Investigators:

Principal: Kenneth D. Burman

Progress & Results:

This study was designed to evaluate the effect on T3 receptors of Somatostatin administration. Somatostatin decreases glucagon levels and has been previously shown that glucagon decreases T3 receptors. Preliminary results of this study indicate that glucagon administration does decrease the number of T3 receptors and T3.Kd, and Ka remain the same, but receptors are diminished Conclusions: Somatostatin decreases glucagon which increases the number of T3 receptors.

Funds Utilized FY-78:

None

Funds Requested FY-79:

Approximately

\$1,000.00

Publications: None yet.

Type of report: Interim.

Work Unit No.: 1397

Title of Project: The Effect of Free Fatty Acids on Serum Reverse T3, and T3.

Investigators:

Principal: Kenneth D. Burman

Objective: To determine free fatty acids influence serum T3 and reverse T3 levels.

Technical Approach: Agents which inhibit are stimulate lypolosis are given to sheep with measurements of T3 and rT3 in blood.

Progress & Results: No animal studies have been done yet.

Conclusions: None.

Funds Utilized, FY-78: None.

Funding Requirement, FY-79:

Personnel	500
Travel	
Rental	
Printing & Reproduction	400
Contractual Svcs.	
Consumable supplies	2,000
Non-expendable equipment	
MEDCASE	

TOTAL	\$2,900
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Publications: None.

Type of report: Interim

Work Unit No.: 1398

Title: Studies on the Pathogenesis of Hypocalcemia in Tumors
Associated with Osteoblastic Metastases.

Investigators:

Principal: Robert C. Smallridge

Associate: H. Linton Wray
John Horton
Richard C. Dimond
Rene Sepulveda
Marcus Schaaf

Objective: To determine whether the hypocalcemia seen in some patients with osteoblastic metastases is due to hypoparathyroidism, a form of secondary hyperparathyroidism, an abnormality in vitamin D metabolism, or some unidentified humoral agent with osteoblastic capability.

Technical Approach: 1. 24 hour urines for calcium, PO4 =, creatinine.

2. Serum for Ca, PO4, Mg, alkaline phosphatase, parathyroid hormone, calcitonin, and vitamin D metabolites.

3. Calcium infusion and PTH infusion.

4. Tissue cultures from marrow biopsies to be tested in vitro for their ability to incorporate 3H-proline into bone collagen.

Progress and Results: This protocol was not approved until 5 June 1978, and no patients have been studied yet.

Conclusions: Deferred.

Funds Utilized, FY-78:

Personnel:

Supplies: Consumable Supplies 2600 \$ 500

Equipment:

Other:

Funding Requirements, FY-79:

Travel	2100	
Personnel:	1100	1,500
Rental	2319	200
Supplies:	2600	1,500
Print & Repro.	2400	100
Contract. Svcs	2572	
Equipment:	3100	=
Other:		TOTAL 6,150

Publications: None

Type of report: Interim.

Work Unit No.: 1399

Title: An assessment of Parathyroid Hormone (PTH) levels
in Normal Subjects and in Patients with Disorders of Calcium
Metabolism.

Investigators:

Principal: Robert C. Smallridge
Richard C. Dimond

Associate: H. Linton Wray
Marcus Schaaf

Objectives: To establish the ranges of serum PTH levels in
normal subjects and patients with metabolic disorders.

Technical Approach: The protocol involves only venipunctures
to obtain blood samples.

Progress and Results: A small number of samples have been
drawn. The radioimmunoassay for PTH is still in the develop-
mental stages.

Conclusions: Deferred

Funds Utilized, FY-78: Consumable Supplies 2600 \$500.00

Personnel:

Supplies:

Equipment:

Travel:

Other:

Funding Requirements, FY-79:

Personnel:	1100	900
Rental	2319	200
Supplies:	2600	1500
Print. & Repro.	2400	100
Equipment:	3100	
Contract. Svcs	2572	
Travel:	2100	300
MEDCASE		2850
Other:		TOTAL 4450

Publications: None

Type of report: Interim

Work Unit No.: 1300-78

Title of Project: The Development of a Radioimmunoassay for 3-Moniodothyronine (3-T1).

Investigator:

Principal: Kenneth D. Burman

Objective: To develop antisera for a radioimmunoassays for various iodothyronines.

Technical Approach: Iodothyronines are conjugated with bovine serum albumin with carbodiimide and rabbits are injected. Bleeds of those rabbits are taken and tested with appropriate I-125 labels to determine if antibodies exist.

Progress & Results: We have been able to develop antibodies to 3,5,T2, 3'T1, and T0 and 3,5'T2. Radioimmunoassay for T3 is still in progress.

Conclusions: Antibodies to various iodothyronines can be made in a specific manner.

Funds Utilized, FY-78:

None.

Funding Requested, FY-79:

Personnel
Travel
Rental
Printing & Reproduction
Contractual Svcs.
Consumable supplies
Non-expendable equipment
MEDCASE

TOTAL

Publications: The development of Radioimmunoassay for 3'5'T2, K.D. Burman, (in press) JCEM.

The development of Radioimmunoassay for 3'T1, R.C. Smallridge, K.D. Burman, et al (in press) JCEM.

3'5'T2, and 3'T1 development of radioimmunoassay and demonstration of in vivo peripheral conversion, R.C. Smallridge, K.D. Burman, and L. Wartofsky, Endocrine Society Annual Meeting, Abstract 102.

Type of report: Interim

Work Unit No.: 1301-78

Title of Project: The Effect of Δ^1 -Testolactone (Teslac) on
5 α -Reductase in Rats.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC

Objectives: To study the ability of Teslac to inhibit the conversion
of testosterone to dihydrotestosterone.

Technical Approach: Immature male rats are castrated and given
silastic capsule containing testosterone, dihydrotestosterone or
estradiol. Equal groups are then injected daily for 1-4 weeks with
Teslac or saline. Blood is obtained at sacrifice for measurement
of steroids. Weights of androgen sensitive organs are also
measured at that time.

Progress & Results: Teslac appears to be anti-androgenic in that
a dose and time dependent inhibition of prostate and seminal ves-
icle growth is present. It appears to inhibit 5 α -reductase ac-
tivity. Measurement of steroids and androgen receptor levels is
in progress.

Conclusions: Teslac is an anti-androgen.

Funds Utilized, FY-78:

2600 Consumable supplies

Funding Requirement, FY-79:

Personnel	750
Supplies, general	2,300
Non-expendable; loose issue	
Printing, publication	200
Rental	200
Contractual Svcs.	100
Equipment	
Travel	400
TOTAL	<hr/> \$3,950

Publications: None.

Type of report: Interim.

Work Unit No.: 1302-78

Title of Project: Effect of obesity in Fasting on Divalent ion, PTH, and Calcitonin Dynamics.

Investigator:

Principal: Kenneth D. Burman
Ira Mehlman

Objective: To determine the changes in calcium kinetics during fasting.

Technical Approach: Patients are admitted to KMU and fasted with PTH and calcium, and calcitonin levels measured periodically.

Progress & Results: No patients have been studied to date.

Conclusions: None.

Funds Utilized FY-78: None.

Funding Requested, FY-79:

Personnel	1,000
Travel	
Rental	
Printing & Reproduction	
Contractual Svcs.	1,000
Consumable Supplies	1,500
Non-expendable equipment	
MEDCASE	
TOTAL	<hr/> \$3,500

Publications: None.

Type of report: Interim.

Work Unit No.: 1303-78

Title of Project: Studies on the Alteration in Drug Metabolism in Hyperthyroidism.

Investigators:

Principal: Robert A. Vigersky, MAJ, MC

Objectives: To determine if changes in metabolism of drugs used to treat hyperthyroidism are due to elevated thyroxine levels, per se, or mediated through beta-adrenergic effects.

Technical Approach: 10 patients will have the half-life and peak plasma levels of dexamethasone (DEX) and Methimazole (MMI) measured after IV injection while hyperthyroid, after 5 days of propranolol, and after becoming euthyroid. Cardiovascular status will be assessed by radionuclide imaging with cardiac output and ejection fraction being measured.

Progress & Results: Project has not yet begun.

Conclusions: None.

Funds Utilized, FY-78:

Funding Requirement FY-79:

Personnel	3,750
Supplies, general	6,000
Non-expendable; loose-issue	
Printing, publication	300
Xerox, office supplies	200
Animals	
Isotopes	600
Equipment	
Travel	500
TOTAL	<u>\$11,350</u>

Publications: None

Type of report: Interim.

Work Unit No.: 1304-78

Title: Radionuclide Assessment of Cardiac Function in Patients
with Acromegaly.

Investigators:

Principal: Robert C. Smallridge

Associate: Sal Rajfer
Robert Kaminsky
James Davia
Marcus Schaaf

Objectives: To determine whether acromegalic patients may have impaired left ventricular function before symptomatic heart disease occurs.

Technical Approach: Left ventricular function is being determined using a multiple gated acquisition (MUGA) scan. This procedure involves the injection of 99m Technitium labeled human serum albumin.

Progress and Results: MUGA scans have been performed on 12 patients with acromegaly. Almost all patients to date have had normal left ventricular ejection fractions despite abnormal echocardiograms in some. The study is not complete, however, and the data have not been formally analyzed.

Conclusions: Deferred.

Funds Utilized, FY-78:

Personnel:

Supplies: 2600 None

Equipment:

Travel:

Other:

Funding Requirements, FY-79: No Funding Requirements in FY-79.

Personnel:

Supplies:

Equipment:

Travel:

Other:

Publications: None

Type of report: Interim.

Work Unit No.: 1305-78

Title: Breast Carcinoma and Thyroid Hormone Receptors

Investigators:

Principal: Robert C. Smallridge

Keith R. Latham

Associate: Arthur Tischler

Objectives: To determine whether thyroid hormone receptors can be identified in human breast carcinomas.

Technical Approach: Breast tumor tissue is frozen in liquid nitrogen, processed to obtain a nuclear pellet, and T3 and T4 receptors determined in a receptor binding assay (Latham, et al, J Biol Chem 251: 7388, 1976).

Progress and Results: Four breast carcinomas have been analyzed, and high affinity nuclear binding sites for T3 were identified in all 4 tumors. Several

Conclusions: We cannot say yet whether these binding sites are in the tumor cells or perhaps in adjacent fibroblasts. Further studies are in progress.

Funds Utilized, FY-78: None 2600 Consumable Supplies

Personnel:

Supplies:

Equipment:

Travel:

Other:

Funding Requirements, FY-79:

Personnel:	1100	400
Rental	2319	200
Supplies:	2600	500
Printing & Reprod.	2400	100
Equipment:	3100	150
Services	2572	200
Travel:	2190	400
	TOTAL \$	1950

Other:

Publications: None

Type of report: Interim.

Work Unit: 1408

Title: Bile Salt Clearance in Chronic Active Hepatitis.

Investigator: COL Lawrence F. Johnson, M.D.

Objective: To ascertain if the Clearance rate of intravenously administered cholyl glycine can reliably relate to clinical parameters in patients with chronic active hepatitis.

Technical Approach: A radioimmunoassay for conjugates of cholic acid will be developed in rabbits by linking cholyl glycine to bovine serum albumin.

Progress and Results: A good radioimmunoassay was developed for conjugates of chenodeoxycholate acid. We continue our work to develop an antibody for conjugates of cholyl glycine.

Conclusions: These assays for conjugates of cholic acid have not been related to date to patients with chronic active hepatitis.

Funds Utilized, FY 78: \$15,482.00

Funds Requested, FY 79: See attached sheet.

Publications: This protocol has resulted in publication of an abstract, a roster presentation at a national meeting and a publication in a peer review journal.

Type of Report: Interim.

FUNDING: Work Unit #1408

	<u>YEARLY TOTAL</u>
(a) Personnel: Chemist - Corinne Maydonovitch	\$13,482.00
(b) Equipment: No additional equipment needed	
(c) Consumable Supplies:	
(1) Rabbits #20 @ \$20.00	400.00
(2) ³ H-cholyl glycine (New England Nuclear) 1.5 mC @ \$104.00 per 250 uC	624.00
(3) Scintillation vials #9 cases case of 500 @ \$45.00	405.00
(4) Hydromix #12 gallon gallon @ \$36.00	432.00
(5) Glycocholic acid 50 grams 25 grams @ \$160.00	320.00
(6) Eppendorf Pipette Tips #5000 1000 @ \$48.00	240.00
(7) Animal Maintenance \$.33/day Average 6 rabbits maintained/year	712.80
(d) Travel to present paper (TDY):	550.00
(e) Consultation Fees:	1,000.00
	<hr/> \$18,165.80

TYPE OF REPORT: Interim

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Work Unit: 1410

Title: Percutaneous (blind) versus Laparoscopic (direct vision) Liver Biopsy in Assessing Chronic Active Hepatitis.

Investigator: COL Lawrence F. Johnson, M.D.

Objective: To ascertain if percutaneous (blind) liver biopsies are adequate in assessing patients with chronic active hepatitis.

Technical Approach: Under the guidelines of this study, patients with chronic active hepatitis who have equivocal percutaneous biopsies will be further evaluated by laparoscopy with biopsy performed under direct vision; and the combined diagnostic accuracy of observation and biopsy will be compared to that of only percutaneous biopsies.

Progress and Results: Eight patients have been entered into the study. In five patients, percutaneous biopsy was accurate as laparoscopy in defining the presence of extensive fibrosis without cirrhosis. One patient had cirrhosis established only by laparoscopy. Two patients had diagnosis of chronic active hepatitis changed to chronic persistent hepatitis after the laparoscopy. To date 33% of the patients had a significant change in their diagnosis as a result of laparoscopy.

Conclusions: Laparoscopy may complement the diagnostic evaluation of patients with chronic active hepatitis.

Funds Utilized, FY 78: None.

Funds Requested, FY 79: Travel - \$400.00
Publication - \$200.00

Publication, FY 78: None.

Type of Report: Interim.

Work Unit: 1415

Title: Esophageal Clearing, Quantitated by Radioisotope Scan.

Investigators:

Principal investigator: COL Lawrence F. Johnson, M.D.

Co-investigators: Andre Dubois, M.D.

MAJ Robert J. Kaminski, M.D.

CAPT Donald O. Castell, M.D, USN

Objective: To quantitate the peristaltic ability of the esophagus to clear a measured bolus of fluid into the stomach.

Technical Approach: Diluted .1 NHCl will be tagged with technecium, and an esophageal clearing profile will be quantitated after each swallow using manometric equipment.

Progress and Results: To date, five patients have been studied. The technique works well. Bethanechol has been shown to improve esophageal acid clearing by increasing esophageal peristaltic pressure.

Conclusions: Data obtained from this protocol represents advancement in the understanding of gastroesophageal reflux disease and supports earlier published observations.

Funds Utilized, FY 78: \$3,185.00 (procurement of Beckman Model 4500 Digital pH Meter, Potentiometric 10-inch Strip Chart Recorder, and Arndorfer Pneumo-Hydraulic Capillary Infusion System).

Funds Requested, FY 79: \$2,500.00.

Publications: None.

Type of Report: Interim.

Work Unit: 1416

Title: Esophageal Emptying in Achalasia: Quantitated by Radioisotope Method.

Investigators:

Principal investigator: COL Lawrence F. Johnson, M.D.

Co-investigator: MAJ Roy K. H. Wong, M.D.

Objective: To quantitate esophageal emptying in achalasia before and after pneumatic dilation.

Technical Approach: To measure esophageal emptying of a solid meal in patients with achalasia. Technecium was tagged to cornflakes and milk and from this an esophageal emptying profile was established.

Progress and Results: The technique proves satisfactory and distinguished asymptomatic control volunteers from symptomatic patients with achalasia. The technique also documented a significant improvement in esophageal emptying after pneumatic dilation.

Conclusions: It is our feeling that this technique will arouse more objective assessment of treatment results in patients with achalasia.

Funds Utilized, FY 78: None.

Funds Requested, FY 79: Same as initial protocol.

Publications: Data from this protocol was presented at the American Gastroenterological Association annual meeting held in Los Vegas, NV, in May 78 (see two attached abstracts).

The following manuscript "Esophageal Emptying in Achalasia Quantitated by a Radioisotope Technique" has been accepted for publication by the American Journal of Digestive Diseases.

Type of Report: Interim.

Work Unit: 1417

Title: Plasma Ligandin in Liver Disease.

Investigator: COL Lawrence F. Johnson, M.D.

Objective: This study proposes to assess plasma ligandin levels as a potentially more sensitive indicator of hepatic information than currently available serum tests.

Technical Approach: All patients having liver biopsies at Walter Reed Army Medical Center have an aliquot of blood drawn and frozen. Plasma serum ligandin content is what is determined by sensitive and quantitative radioimmunoassay technique. Correlations between pathologic diagnosis, enzyme values and ligandin levels will be made by standard statistical techniques.

Progress and Results: One hundred sixteen samples of serum have been forwarded to the Albert Einstein College of Medicine in New York for ligandin determinations. Results are pending.

Conclusions: Not available.

Funds Utilized, FY 78: None.

Funds Requested, FY 79: Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit: 1418

Title: Preliminary Clinical Evaluation of Triamcinolone Acetonide Retention Enemas in the Treatment of Distal Ulcerative Colitis.

Investigators:

Principal investigator: MAJ Stephen R. Siegel, M.D., MC

Co-investigators: MAJ Joseph S. Rice, M.D., MC

LTC Samuel Goodloe, M.D., MC

Objective: To evaluate on a preliminary basis the efficacy of a new high potency steroid retention enema to improve patients with distal ulcerative colitis that have been refractory to standard hydrocortisone retention enemas and oral sulfasalazine.

Technical Approach: This was a random double blind study involving two treatment arms with triamcinolone acetonide: 5 mg versus 2 mg aqueous retention enema.

Progress and Results: Four patients were accessioned into the protocol, their forms completed and submitted to Rowell Laboratories, Inc.

Conclusions: All patients had a favorable response to triamcinolone acetonide retention enemas; and, from the small sampling, it was difficult to tell whether the 2 or 5 mg dose gave the best response. The favorable responses in this preliminary study would warrant a larger double blind random study testing triamcinolone versus conventional steroid enemas in the treatment of ulcerative colitis. It is my understanding that Rowell Laboratories contemplates a study of this nature at a future date.

Funds Utilized, FY 78: None.

Funds Requested, FY 79: None.

Publications: None.

Type of Report: Completed.

Work Unit: 1419

Title: Cricopharyngeal Bar: A Video Manometric Study.

Investigators:

Principal investigator: COL Lawrence F, Johnson, M.D., MC

Co-investigators: MAJ Roy K. H. Wong, M.D., MC

MAJ David J. Curtis, M.D., MC

Objective: To study the functional significance of a cricopharyngeal bar.

Technical Approach: This is a synchronized manometric/video tape fluoroscopic study of swallowing disorders of the hypopharynx, cricopharyngeus and upper esophagus.

Progress and Results: A sophisticated, slow motion (1 frame per second) video tape machine has been procured by the Department of Radiology and the necessary cables have been installed to have WRAMC TV record the data. The special cricopharyngeal catheter has been made and works satisfactorily in a control volunteer. With all involved investigators in the New Treatment Facility, it is anticipated that this study will accession patients shortly.

Conclusions: None.

Funding Utilized, FY 78: None.

Funding Requested, FY 79: Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit: 1420

Title: Adenyl Cyclase and Guanyl Cyclase Activity in the Cat Esophagus.

Investigators:

Principal investigator: MAJ Roy K. H. Wong, M.D.

Co-investigators: COL Lawrence F. Johnson, M.D.

CAPT Donald O. Castell, M.D., USN

Objective: To correlate adenyl cyclase and guanyl cyclase activity with lower esophageal sphincter contraction and relaxation.

Technical Approach: Same as initial protocol.

Progress and Results:

1) Since receiving funds for the above study, the following progress has been made. A pilot study was done in 5 rabbits where adenyl cyclase activity was determined in serial sections of the rabbit esophageal muscle. The data indicates that significantly higher levels of adenyl cyclase are present in the region of the lower esophageal sphincter (LES) as compared to the rest of the esophagus. Subsequently, we began using cats as our animal model, but realized after sacrificing five cats that the cat esophagus and LES was technically too difficult to isolate. At present, we are in the process of obtaining opossums to be utilized as our animal model. We have decided to use opossums because: 1) technically, the opossum esophagus is easier to isolate; and 2) the muscular anatomy of the opossum is closer to the human.

2) In conjunction with the above project, a combined study with WRAIR was undertaken. An abstract was submitted to Gastroenterology and is included in this report. The same abstract was presented by Principal Investigator at the William Beaumont Gastrointestinal Symposium. It is hoped that this work will be eventually published.

Conclusions: Significant progress has been made in mastering the techniques of the adenyl and guanyl cyclase assay. Significant results have been found in the rabbit esophagus, but at present time, we are in the process of using opossums which are a more acceptable animal model for this study. We feel that funding for this project should be continued, as ongoing progress has been made.

Funds Utilized, FY 78: Approximately \$2,500.00 has been used over the last year in animals and equipment.

Funding Requested, FY 79: Over the next year, another \$2,500.00 is needed for the funding of animals and equipment.

Publications: Attached.

Type of Report: Interim.

Work Unit: 1421

Title: Immune Characteristics of Peripheral Blood Lymphocytes in Patients on Cimetidine.

Investigators:

Principal investigator: MAJ Robert Reid, M.D., MC

Objective: To determine if the function of human peripheral blood lymphocytes is altered during treatment with Cimetidine (Tagamet), a histamine type-2 receptor blocker.

Technical Approach: To study the classification and functional characterization of peripheral blood lymphocytes in patients receiving Cimetidine. Multiphasic immunologic testing as outlined in protocol will be performed.

Progress and Results: Ten patients have been accessioned into the study, and preliminary review of the data to date would indicate that there is no immunologic impairment of patients on Cimetidine as studied in this protocol.

Conclusions: Not applicable.

Funding Utilized, FY 78: None.

Funding Requested, FY 79: Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit No.: 1422

Title: The Sequential Staging of the Liver in Hodgkin's Disease With Laparoscopy and Laparotomy.

Investigators:

Principal Investigator:

MAJ David A. Peura, M.D.
Staff, Gastroenterology Service
(Replacing MAJ Joseph S. Rice, M.D.
who has been transferred to Fitzsimons AMC, Denver, CO)

Co-investigators:

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service

COL Richard M. Hirata, M.D.
Chief, General Surgery Service
(Replacing COL Robert W. Muir, M.D.)

MAJ Martin D. Weltz, M.D.
Fellow, Hematology-Oncology Service

Objective: To evaluate the role of laparoscopy in clinical Stage III or IV Hodgkin's disease patients.

Technical Approach: See Plan Section of original protocol (attached).

Progress and Results: Sixteen patients were studied and sequentially staged in the manner similar to that described under the Technical Approach. One of the patients was shown to have positive liver at the time of laparoscopy, thus, did not undergo further surgical staging. Twelve patients were found to have no liver involvement at time of laparoscopy, and none were subsequently found to have involvement at the time of surgery. Three patients were found to have no involvement of the liver at the time of laparoscopy, but further staging laparotomy was not done.

Conclusions: Laparoscopy appears to be of benefit in the sequential staging of Hodgkin's disease, in that laparoscopic results appear favorably with those found at subsequent surgical staging. One patient in the study group was saved a subsequent surgical staging when he was noted to have involvement at the time of laparoscopy. Further evaluation of the study population is needed before final statistically significant conclusions may be reached.

Funds Utilized FY 78: None.

Funding Requested FY 79: None.

Publications: None.

Type of Report: Interim.

Work Unit No.: 1423

Title of Project: A Study of Trifluoroisopropyl Cyanoacrylate Polymer (MBR 4197) in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum

Investigators:

Principal: MAJ David A. Peura, M.D.
Staff, Gastroenterology Service

Co-investigators: LTC Edward L. Burkhalter, M.D.
Fellow, Gastroenterology Service

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service

Gastroenterology Service, Department of Internal Medicine, Walter Reed Army Medical Center, Washington, D.C. 20012.

Objectives: To determine if the polymer is effective in preventing further bleeding in stomach and duodenal ulcers.

Technical Approach: Comparison of a control group and a group treated with the polymer. The two groups will be comparable except for treatment with polymer. Blood transfusion, hematocrit and number of patients going to surgery will be accessioned. The goal is to have 20 patients in the protocol.

Progress: The protocol was begun on 1 June 1978. One patient has been included in the protocol as of 11 Sept 1978; and this patient is a control.

Conclusion: No conclusion can be made at this time.

Funds 78: None.

Funds 79:

A) Personnel: See Principal Investigators.

B) Equipment: None.

C) Consumable Supplies: \$100.00

1. Sterile saline

2. CO₂ tanks

Work Unit No. 1423

D) Travel: Presentation of paper at national
scientific meeting \$300.00

E) Modifications of Facilities: None

F) Other: Reprints \$250.00

Publications: NA

Type of Report: Interim.

Work Unit: 1424

Title: A Double Blind Study of Long Term Maintenance Cimetidine (SKF 92334) Therapy on Gastroesophageal Reflux Disease - Protocol B07.

Investigators:

Principal investigator: MAJ Roy K. H. Wong, M.D.

Co-investigator: COL Lawrence F. Johnson, M.D.

Objective: To determine if Cimetidine, an inhibitor of gastric acid secretion, will, on long term maintenance therapy, benefit patients with acid gastroesophageal reflux over that of conventional medical therapy.

Technical Approach: Same as initial protocol.

Progress and Results: Since the inception of this protocol (June 78), three patients are presently in the closed phase of the protocol (coded medicine). We have screened 20 patients thus far, and five patients are scheduled to enter the closed phase of the protocol in Jan 79. A total of 15 patients in the closed phase of the protocol is required from each center.

Conclusions: If the trend continues, our quota of patients for this protocol should be obtained by April 79.

Funds Utilized, FY 78: None

Funding Requested, FY 79: Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit No.: 1425

Title: Pulmonary Aspiration From Gastroesophageal Reflux Defined by Pulmonary Scintiscan and Overnight Intra-esophageal pH Monitoring.

Investigators:

Principal Investigator:

MAJ Steven S. Shay, M.D.
Fellow, Gastroenterology Service

Co-investigators:

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service

LTC Mark R. Stein, M.D.
Staff, Allergy/Immunology Service

MAJ Robert J. Kaminski, M.D.
Asst Chief, Nuclear Medicine Service

From Walter Reed Army Medical Center, Washington, D.C.

Objective: To document the occurrence of pulmonary aspiration from nocturnal gastroesophageal reflux.

Technical Approach: Patients with symptoms of both pulmonary disease and gastroesophageal reflux are being evaluated to develop a test to see which of the patients with chronic pulmonary disease has aspiration on the basis of gastroesophageal reflux. Patients are admitted on the morning of Day 1 and a manometry catheter is placed into the esophagus for location of the lower esophageal sphincter to make sure the patients are capable of making acid. Later in the day, patients are started on pH monitoring and is continued until the following morning. This is the best parameter of reflux. Prior to bedtime, the patients are dosed with 5 mci of radioactive technetium sulfa colloid Tc⁹⁹. On the morning of Day 2, the patients report to Nuclear Medicine for a lung and abdominal scan for location of technetium. The patients are then questioned regarding their symptomatology during the night - reflux and aspiration - and comparison is made by a direct Chi² analysis to the objective criteria of the esophageal reflux by pH monitoring, aspiration by lung scan.

Progress and Results: Seven patients have been entered into this study at this point. The patients studies have met the criteria of underlying or overt pulmonary disease, and two have had significant reflux by manometry study. To date, we have not had positive scintiscan. Despite initial negative results, we are planning to study patients with more symptomatology of reflux in hopes of finding gross reflux on pulmonary scan.

Annual Progress Report - No. 1425

Conclusion: Pending further patient study.

Funds Utilized, FY 78: None.

Funding Requested FY 79: See protocol (attached).

Publications: None to date.

Type of Report: Interim.

Work Unit No.: 1426

Title of Project: Effect of Indomethacin on Experimentally Induced Acid Stricture on the Cat Esophagus

Investigators:

Principal Investigator: MAJ David A. Peura, M.D.
Gastroenterology Service
(Replacing MAJ Joseph S. Rice, M.D.,
who was transferred to Fitzsimmons
Army Medical Center, Denver, CO)

Co-investigators: COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service
Walter Reed Army Medical Center

CAPT Donald O. Castell, M.D., USN
Chief, Department of Medicine
National Naval Medical Center

LTC Robert J. Beattie, D.V.M.
Chief, Department of Animal Resources
Walter Reed Army Institute of Research

Objective: To determine if indomethacin has an affect on acid stricture formation on the cat esophagus.

Technical Approach: See Study Plan on original protocol (attached).

Progress and Results: Three cats were studied under the protocol; two controls, one indomethacin cat. Data was obtained and compared to a nontreated control animal. Both control animals developed severe strictures. Indomethacin treated cat also developed a stricture but not to the degree of the control animals. Pathological results showed evidence of gross esophagitis with some early fibrosis; however, collagen contents were analyzed and did not seem statistically different between control, indomethacin, or untreated control animal. Several observations were made. First, nutrition was a problem in the strictured animals since the NG tube could not be passed; thus, an alternate route of nutrition was needed in the animal model. Second, there appeared to be suggestion of some stricture inhibition by indomethacin, and further evaluation is warranted using higher doses of this medication. Third, possible reduction of stricture might be obtained using other medication, such as synthetic prostoglandins or collagen inhibitors such as colchicine.

Annual Progress Report - No. 1426

Conclusions:

- 1) The acid infused cat esophagus is good stricture model, since all treated cats developed anticipated stricturing.
- 2) Further investigation is warranted using higher doses of indomethacin.
- 3) Alternative drugs, such as synthetic prostoglandins or collagen inhibitors may prove useful in preventing strictures in the acid infused model.
- 4) Further studies will be carried out in cats with indwelling gastrostomies to eliminate the problem of inadequate nutrition.

Funds Utilized, FY 78: Funds utilized were those necessary to procure and maintain the three cats used.

Additional Funding Requirement, FY 79: No additional funds will be necessary; however, remainder of the funds that were provided for under the original protocol for FY 78 will be needed to complete the study.

Publications: None.

Type of Report: Interim.

DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-MH

SUBJECT

Annual Progress Report, FY 78 - Clinical Investigation Program, Oncology Section, Hematology-Oncology Service

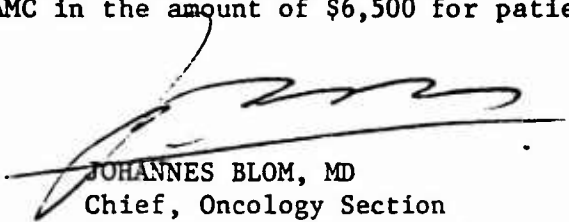
TO C, Clin Invest Svc

FROM C, Onc Sec, Hem-Onc Svc DATE 24 Apr 79

CMT 1

/mjh/61755

1. The Oncology Section, Hematology-Oncology Service, continued to participate in studies of the Cancer and Leukemia Group B (CALGB) of experimental and standard drugs, singly and in combinations, and in combination with radiation therapy, in patients with various neoplastic diseases. New WRAMC protocols were initiated during FY 1978 and others were continued from previous years.
2. All diagnoses of malignancy were substantiated by histological examination of biopsy material. All patients were informed of the experimental nature of the therapy and were provided information related to the toxicity which might be expected from therapy. The informed consent was signed by each patient, parent, or guardian.
3. All protocols were reviewed by the Walter Reed Army Medical Center Clinical Investigation and Human Use Committees and forwarded to the Human Use Review Office, Office of the Surgeon General, for approval in compliance with AR 40-7.
4. Funds in the amount of \$67,425 were received from the National Cancer Institute through an Interagency Agreement. These funds were used for 50% of the salary of the Principal Investigator, two medical record technicians, patient travel, and physician travel to CALGB meetings. Because of the ceiling on travel funds imposed by the NCI, additional funds were received from WRAMC in the amount of \$6,500 for patient travel.


JOHANNES BLOM, MD
Chief, Oncology Section
Hematology-Oncology Service

Work Unit No.: 1516

Title of Project: ALCB Protocol #7291 - Add. #2: Intergroup rhabdomyosarcoma study; role of postoperative radiotherapy and combinations of dactinomycin, vincristine, cyclophosphamide and adriamycin in childhood rhabdomyosarcoma by Acute Leukemia Group B, Southwestern Cancer Chemotherapy Study Group and Childrens Cancer Study Group A.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

- Objectives:
1. To determine wheather postoperative radiotherapy prevents local recurrence and improves the survival rate after what appears to be complete surgical removal of the localized tumor.
 2. To compare duration of remission, recurrence and survival of patients treated with vincristine and dactinomycin with those treated with vincristine, dactinomycin and daily oral cyclophosphamide.
 3. To compare in terms of response to treatment, length of remission, percentage exhibiting recurrence and survival of the effectiveness of vincristine, dactinomycin and high pulse doses of cyclophosphamide to the same drug combination plus adriamycin for the treatment of patients with gross residual disease at the time of diagnosis.

Technical Approach: Patients are divided into four groups:

Group 1 - localized disease completely removed

Group 2 - grossly removed tumor with microscopic residual disease

Group 3 - incomplete removal of tumor
or biopsy with gross residual disease

Group 4 - distant spread of disease
present at onset

Patients are randomized according to
their disease group and treatment
started within 72 hours of surgery.

The patients in group 1 will be
randomized between regimen A and B,
patients in group 2 will be randomized
between regimen C and D (regimen
D is the same as regimen B), and
patients in group 3 and 4 will be
randomized between regimen E and F.

Regimen A: vincristine, 2 mg/M²
(maximum dose 2.0 mg)
IV weekly for 12 doses
plus
dactinomycin 0.015 mg/kg/day
(max. 0.5 mg) IV for 5
days to be repeated 12,
24, 36 and 48 weeks plus
cytoxan 2.5 mg/kg/day
orally starting on day
42 and continuing it up
through 24 months

Regimen B: radiotherapy to the tumor
bed after surgery plus
chemotherapy as outlined
in regimen A

Regimen C: radiotherapy to the tumor
bed after surgery plus
dactinomycin 0.015 mg/kg/day
(max. 0.5 mg) IV for 5
days to be repeated at
9, 18, 27, 36 and 45
weeks plus
vincristine 2 mg/M² (max.
2 mg) IV weekly for six
doses

Regimen E: vincristine 2 mg/M^2
(max. 2 mg) IV weekly
for 12 doses plus
dactinomycin 0.015 mg/kg/day
(max. 0.5 mg) IV for 5
days to be repeated 18,
30, 42 and 54 weeks plus
cytoxan 10 mg/kg/day IV
for 7 days, a second
seven day course to be
given by mouth at 13
weeks
cytoxan 2.5 mg/kg/day p.o.
from 21st week through
the 24th month of therapy
plus
radiotherapy to the tumor
bed as well as to the
areas of spread to be
started at six weeks

Regimen F: vincristine 2 mg/M^2 (max.
2.0 mg) IV weekly for 12
doses plus
dactinomycin 0.015 mg/kg/day
(max. 0.5 mg) in the vein
for 5 doses to be repeated
at 2, 33, 45 and 57 weeks
plus
cytoxan 10 mg/kg/day IV
for 7 days a second 7 day
course by mouth to be
started at 13 weeks
cytoxan 2.5 mg.kg.day by
mouth from the 24th week
to the 24th month of
therapy plus
adriamycin 50 mg/M^2 IV
at 5, 18, 27, 39 and
51 weeks. This will
reduce to 30 mg/M^2 if
a large bone marrow
volume is to be irradiated
(maximum total dose 600
 mg/M^2) plus
radiotherapy to the tumor
bed as well as to the
areas of spread to be
started in six weeks

Progress & Results: WRAMC entered eleven patients. One was lost to follow-up shortly after entry on the study. One patient expired with progressive disease on day 117. One relapsed on day 660 and one on day 323. Six patients remain without evidence of disease from 340 to 1460 days.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1517

Title of Project: ALGB Protocol 7331 - Aid. O: Hydroxyurea (NSC 32055), 6-Mercaptopurine (NSC 755), and Prednisone (NSC 10023) with or without Vincristine (NSC 67574) and Daunorubicin (NSC 84151) in the Treatment of the Resistant Phase of Chronic Granulocytic Leukemia. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To assess the effectiveness of the combination of hydroxyurea, 6-MP and prednisone with or without vincristine in the resistant phase of chronic granulocytic leukemia for remission induction and maintenance.
 2. To assess the effectiveness of daunorubicin as a consolidation agent.

Technical Approach:

1. Induction:

Regimen I - Hydroxyurea 30 mg/kg/day p.o. in one dose plus
6-MP 3 mg/kg/day p.o. in two divided doses plus
Prednisone 0.75 mg/kg/day p.o. in two divided doses

Regimen II- Hydroxyurea 30 mg/kg/day p.o. in one dose plus
6-MP 3 mg/kg/day p.o. in two divided doses plus
Prednisone 0.75 mg/kg/day p.o. in two divided doses plus
Vincristine 1.5 mg/m² I.V. every week for four doses

2. Consolidation:

Regimen A - Daunorubicin 60 mg/m² daily for two days plus
Prednisone 0.25 mg/kg/day p.o. in two divided doses

Regimen B - No consolidation

3. Maintenance: Will continue until there is recurrence of disease.

Regimen I - Hydroxyurea 7 mg/kg/day p.o. one daily dose in a.m. plus
6-MP 0.7 mg/kg/day p.o. one daily dose in a.m. plus
Prednisone 0.25 mg/kg/day p.o. in two divided doses

Regimen II- Hydroxyurea 7 mg/kg/day p.o. one daily in a.m. plus
6-MP 0.7 mg/kg/day p.o. one daily in a.m. plus
Prednisone 0.25 mg/kg/day p.o. in two divided doses plus
Vincristine 1.5 mg/m² in the vein once a month.

Progress & Results: WRAMC has entered four patients. One patient was disqualified, one expired on day 39, and one expired on day 65. One patient went into complete remission, but had prolonged hypocellularity of the bone marrow. After recovery, she was placed on non-random maintenance regimen. She relapsed on day 665.

Conclusions: There is no difference between the two induction regimens and responses are unsatisfactory and rather short. This protocol was replaced by CALGB protocol 7531 on 20 August 1975.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

1518

Title of Project: AL33 Protocol 7383 - Add. O: Clinical Trial of VP-16-213 (NSC 141540)(4'-dimethyl-epipodophyllo-toxin-3-D-ethylidene-glucoside) in Advanced Neoplastic Disease. A Phase II Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To examine the antitumor effect (remission induction and maintenance) of VP-16-213 in a broad spectrum of metastatic tumors.

Technical Approach:

Regimen I - VP-16 60 mg/m² twice weekly for four weeks

Regimen II - VP-16 90 mg/m² twice weekly for four weeks.

Progress & Results: WRAMC entered six patients. One was found dead at home five days after he was entered on the study. The other five patients did not respond and had progressive disease and subsequently expired.

ALGB has entered 382 patients, 346 were evaluable at the last analysis in September 1976: Complete and partial response rates with 60 mg and 90 mg were 9% and 12% respectively. The response rate with the 135 mg regimen was 6%. Lymphomas and GI malignancies are still the most responsive tumors. The protocol was discontinued in September 1976.

Conclusions: This drug has some activity in lymphomas and malignancies of the GI tract.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: None

Type of Report: Terminated

Rock Unit No.: 1519

Title of Project: ALGB Protocol 7361: Multiple Myeloma Resistant to 1-phenylalanine Mustard Treated with Cyclophosphamide (Cytosan)(NSC 26271), Prednisone (NSC 10023) and 1,3-bis-(2-chloroethyl-1-nitrosourea)(BCNU)(NSC 409962).

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine whether patients previously treated with 1-phenylalanine mustard but with recurrent active disease will respond to other alkylating agents (cyclophosphamide and BCNU) and prednisone.

Technical Approach:

Regimen I - Cyclophosphamide 600 mg/m^2 I.V. on day 1 plus
Prednisone 0.6 mg/kg orally daily for 14 days (in 3
equally divided doses beginning on day 1)
 0.4 mg/kg orally daily for 14 days
 0.25 mg/kg orally daily for 14 days

Then every 6 weeks:

Cyclophosphamide 600 mg/m^2 I.V. x1 plus
Prednisone 0.6 mg/kg/day x7

Regimen II - Cyclophosphamide 300 mg/m^2 I.V. on day 1 plus
BCNU 100 mg/m^2 I.V. on day 1 plus
Prednisone 0.6 mg/kg orally daily for 14 days (in 3
equally divided doses beginning on day 1)
 0.45 mg/kg orally daily for 14 days
 0.25 mg/kg orally daily for 14 days

Then every 6 weeks:

Cyclophosphamide 300 mg/m^2 I.V. x1 plus
Prednisone 0.6 mg/kg/day x7
BCNU 100 mg/m^2 I.V. x1

Progress & Results: WRAMC has entered seven patients; three patients had responses with subsequent progressive disease on day 308, 394 and 548. Three patients had no response and went off study on day 88, 111, and 400. One patient had no change and subsequently expired.

Conclusions: Responses with cytoxan and prednisone and BCNU are possible in patients who are resistant to l-phenylalanine mustard and seem to be somewhat better than responses to cytoxan and prednisone alone.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: Manuscript submitted

Type of Report: Entry of new patients on the protocol was stopped on 3 December 1976. This constitutes the final report.

Work Unit No.: 1520

Title of Project: ALGB Protocol #7411 - Add. #2: Combination chemotherapy in induction for standard risk and combination chemotherapy plus cranial irradiation plus daunorubicin for increased risk followed by maintenance with continuous vs. intermittent 6-MP plus methotrexate reinforcement and subsequent immunotherapy. Activated 18 April 1974.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick Ruymann, M.D., LTC, MC

- Objectives:
1. To assess the role of early cranial radiation in the control of CNS and systemic leukemia by randomly allocating its use.
 2. To introduce the concept of more vigorous induction and reinforcement therapy for a group of children considered to be at increased risk; older or younger age (after the 8th birthday or before the 2nd) and/or high leukocyte count (over 30,000), and test whether the addition of daunorubicin will favorably affect the frequency and/or the duration of complete remission in such patients.
 3. To compare the effectiveness of three reinforced maintenance regimens:
 - A. Continuous combined oral 6-MP daily and oral MTX weekly.
 - B. Intensification with 5-day courses of combined oral MTX weekly.
 - C. Intensification with 5-day courses of oral MTX alone.
 4. To be prepared to introduce immunotherapy in maintenance phase regimens at random.

Technical Approach: Patients are stratified in two risk categories:

Standard Risk: age is after the 2nd and before the 8th birthday and a total white count of less than 30,000.

Increased Risk: age is before the 2nd or after the 8th birthday or the total white blood count is equal to or greater than 30,000.

Patients at standard risk will be allocated to regimens 1 or 2. Patients at increased risk will be allocated to regimens 2 or 3.

Regimen I: vincristine $2.0 \text{ mg/M}^2/\text{week}$ IV for 4 weeks on days 1, 8, 15 and 22
plus
prednisone $40.0 \text{ mg/M}^2/\text{day}$ p.o. for 4 weeks (days 1-28), then taper to $20.0 \text{ mg/M}^2/\text{day}$ for 2 days, $10 \text{ mg/M}^2/\text{day}$ for 2 days, $5.0 \text{ mg/M}^2/\text{day}$ for 2 days, $2.5 \text{ mg/M}^2/\text{day}$ for 2 days, then stop prednisone
plus
methotrexate 12.0 mg/M^2 q 2 weeks IT for six doses on days 1, 15, 22, 43, 50 and 57
plus
l-asparaginase 1000 IU/kg/day IV for ten consecutive days from day 29 through 38

Regimen II: vincristine $2.0 \text{ mg/M}^2/\text{week}$ IV for 4 weeks on days 1, 8, 15 and 22
plus
prednisone $40.0 \text{ mg/M}^2/\text{day}$ p.o. for 4 weeks (days 1-28), then taper as Regimen I.
plus
methotrexate 12.0 mg/M^2 q 2 weeks IT for six doses on days 1, 15, 22, 43, 50 and 57 (last three injections coincide with cranial irradiation)
plus
l-asparaginase 1000 IU/kg/day IV for ten consecutive days from day 29 through 38
plus
cranial irradiation beginning on day 43 (after completion of l-asparaginase) 2400 rads of cranial irradiation over 16 days to day 58.

Regimen III: vincristine $2.0 \text{ mg/M}^2/\text{week}$ IV
for 4 weeks on days 1, 8, 15
and 22
plus
prednisone $40.0 \text{ mg/M}^2/\text{day}$ p.o.
for 4 weeks (days 1-28) and then
taper as in Regimen I
plus
methotrexate 12.0 mg/M^2 q 2 weeks
IT for six doses on days 1, 15,
22, 43, 50 and 57 (last three
injections coincide with cranial
irradiation)
plus
daunorubicin $45.0 \text{ mg/M}^2/\text{day}$ IV for
3 days on days 1, 2 and 3 for
those 2 years and over and
 $22.5 \text{ mg/M}^2/\text{day}$ IV for 3 days on
days 1, 2 and 3 for those under
2 years of age
plus
l-asparaginase 1000 IU/kg/day IV for
ten consecutive days from day
29 through 38
plus
cranial irradiation beginning on day
43 (after completion of l-asparagi-
nase) 2400 rads of cranial irradia-
tion over 16 days to day 58.

Maintenance phase:

Regimen A: continuous oral 6-MP and MTX:
 $6\text{-MP } 90.0 \text{ mg/M}^2/\text{day}$ orally
plus
 $\text{MTX } 15.0 \text{ mg/M}^2/\text{week}$ orally on
the 1st day of each week
reinforce with vincristine and
prednisone at monthly intervals
for five months, thereafter two
week reinforcement treatments
are given after the sixth month
and every three months
thereafter. The doses are as
follows:

vincristine 2.0 mg/M^2 IV
plus
prednisone $40.0 \text{ mg/M}^2/\text{day}$ p.o. for
one week beginning with the
vincristine injections -
(do not taper). When two week
reinforcements are given,
prednisone continues for two
weeks and then is tapered.

Patients induced on regimen 3 with
daunorubicin will receive
daunorubicin as part of the
reinforcement course at the 13th
and 25th week of maintenance,
 $45.0 \text{ mg/M}^2/\text{day}$ IV x 2 beginning
on the 1st day of the vincristine
plus prednisone reinforcement.

Regimen B: intermittent intensification oral 6-MP
and oral MTX:

6-MP $200 \text{ mg/M}^2/\text{day}$ orally for five
days

plus

MTX $7.5 \text{ mg/M}^2/\text{day}$ orally for five
days

wait nine days and then repeat,
wait nine days and then repeat for
a third course

reinforce with vincristine and
prednisone after every third
course:

vincristine 2.0 mg/M^2 IV on days
1 and 8 for two week reinforce-
ment treatment

plus

prednisone $40.0 \text{ mg/M}^2/\text{day}$ p.o. for
2 weeks and then taper with each
vincristine reinforcement

Patients induced on regimen 3 with
daunorubicin should receive dauno-
rubicin as part of the reinforcement
course at the 15th and 31st weeks of
maintenance, $45.0 \text{ mg/M}^2/\text{day}$ IV x 2
beginning on the first day of
vincristine and prednisone reinforce-
ment

Regimen C: Intermittent intensification oral MTX alone:

MTX 15.0 mg/m²/day orally for 5 days

Wait 9 days and repeat

Wait 9 days and repeat for a third course

Reinforce with vincristine and prednisone after every third course:

Vincristine 2.0 mg/m² I.V. on days 1 and 8 for 2-week reinforcement treatment, plus

Prednisone 40.0 mg/m²/day p.o. for 2 weeks and tapered with each vincristine reinforcement

Patients induced on regimen 3 with Daunorubicin should receive Daunorubicin as part of the reinforcement course at the 15th and 31st weeks of maintenance, 45.0 mg/m²/day I.V. x2 beginning on the first day of vincristine plus prednisone reinforcement.

Progress & Results: WRAMC entered 16 patients. One patient was invalidated because review of the material was more in favor of AML rather than ALL. Ten patients had a complete remission, one of whom relapsed on day 56 and the other on day 738. Two were not evaluable for maintenance. The remaining six patients are still in remission from 729 to 1370 days. One patient had a partial remission, and then moved to another area where he is being followed by another member of CALGB. Three patients had progressive disease.

Conclusions: The remission induction durations and CNS relapse are essentially equivalent in the various treatment regimens.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: None

Type of Report: Entry of patients was discontinued on 12 November 1976.

Title of Project: ADIS Protocol 7391 - Ad. 0: Clinical Trial of Radiotherapy and Chemotherapy (Cyclophosphamide (NSC 26271), Vincristine (NSC 67574) and Actinomycin-D (NSC 3053)) in Managing Non-Metastatic Ewing's Sarcoma.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M. D., LTC, MC

Objectives:

1. Compare the time interval from clinically localized tumor to appearance of metastases using (a) irradiation of the primary tumor only, (b) irradiation of the primary tumor plus systemic chemotherapy (cyclophosphamide, vincristine and dactinomycin)
2. Compare the time interval from clinically localized tumor to appearance of metastases using: (a) localized irradiation of the primary tumor plus chemotherapy, (b) irradiation of the primary tumor plus chemotherapy plus bilateral pulmonary irradiation.
3. Document the incidence and time of appearance of local recurrence in all patients included in the protocol regimens.
4. Document the total survival time of patients treated by all protocol regimens.
5. Document and evaluate the pattern of organ metastases for all protocol patients who develop metastases so future studies will result in programming improved means of therapy.

Technical Approach:

Initial Plan:

Regimen I - Vincristine 15 mg/m²/week I.V. x6 plus
Cyclophosphamide 500 mg/m² I.V. x6 plus
Radiotherapy to the lesion

Regimen II - Vincristine $1.5 \text{ mg/m}^2/\text{week}$ x6 plus
Cyclophosphamide $500 \text{ mg/m}^2/\text{week}$ I.V. x6 plus
Radiotherapy to the lesion and both lung fields

Continuation Plan: Actinomycin-D 15 mcg/kg daily I.V. x5 at 3 months; after one week's rest vincristine and prednisone are given from the third through the seventh week. These 7-week courses are repeated every 3 months for a total of 6 in 18 months.

Progress & Results: WRAMC entered seven patients. One relapsed on day 582. One went off study shortly after entry, and a third patient relapsed. One patient died on day 356; one patient is free of disease on day 382, one on day 58 and one patient is too early for evaluation.

Conclusions: The arms employing adriamycin and bilateral pulmonary radiotherapy are both superior to the arm with vincristine, actinomycin-D, cyclophosphamide and radiation of the primary tumor site alone. Delayed pulmonary toxicity from radiation therapy may occur only in patients who receive actinomycin-D in addition to radiation therapy. The sites of greatest risk appear to be the pelvis and proximal lesions.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit

Title of Project: ALGB Protocol #7451 - Add. #0: Combination radiotherapy and chemotherapy of stage III Hodgkin's disease. (Phase III)

Investigators:

Principal: Johannes Blom, M.D.

Associate: Henry Keys, MAJ, MC, USA

- Objectives:
1. To compare long-term, multiple-agent chemotherapy either alone or in combination with total nodal radiotherapy with total nodal radiation therapy alone.
 2. To compare tolerance of patients to these treatments of various intensities.
 3. To compare the quality of response, duration of response and survival rates of the therapeutic groups.
 4. To compare tolerance of therapy for patients with and without prior splenectomy for staging.
 5. To study patterns of relapse in the various study groups.

Technical Approach: Regimen I: total nodal radiation therapy with the mantle port above the diaphragm and inverted "Y" below the diaphragm plus the spleen or splenic pedicle area and optionally the porta hepatis.

Regimen II: chemotherapy consisting of:
vincristine 1.4 mg/M²/week IV x 2 with
a maximum dose of 2.0 mg
plus
procarbazine 50.0 mg on day 1 p.o.
100.0 mg on day 2 p.o.
100.0 mg/M²/day on days
3-14 p.o.
plus
BCNU 80.0 mg/M² IV on day 1

Each course will consist of 2-weeks
treatment and 2-weeks rest.

The 2nd and 3rd course will be as described above with the deletion of prednisone.

The 4th course is the same as the 1st course with prednisone included.

The 5th and 6th course is the same as the 2nd and 3rd course - vincristine/ procarbazine/BCNU with the prednisone.

Maintenance therapy will be given for 3 years consisting of:

chlorambucil 6.0 mg/M²/day p.o.

Regimen III: Chemotherapy followed by radiation therapy.

Six cycles of chemotherapy as outlined under regimen II will be followed by a 2-month rest period and then total nodal radiation as described under regimen I.

No maintenance drugs will be given.

Progress & Results: WRAMC has entered 12 patients, 4 of whom obtained complete remission, 5 a partial remission and 2 patients were disqualified; one patient is too early for evaluation. One patient with a complete remission relapsed on day 203 and one on day 780. The other 2 complete remissions remain in remission 380 and 690 days respectively. Duration of partial remissions continues from 455 to 555 days.

Conclusions: Too early.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1533

Title of Project: ALGB Protocol 7461 - Add. 3: Primary Treatment of Multiple Myeloma: Comparison of L-PAM (NSC 8806) plus Prednisone (NSC 10023) and BCNU (NSC 409962) plus Prednisone and CCNU (NSC 79037) plus Prednisone with or without Intermittent Vincristine (NSC 67574) and Prednisone. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To compare the relative response inducing capabilities of CCNU plus prednisone, BCNU plus prednisone, and L-PAM plus prednisone in multiple myeloma.
 2. To study the effectiveness of intermittent reinforcement doses of vincristine and prednisone added to the therapies described under 1 in multiple myeloma.

Technical Approach:

Regimen I - L-PAM 150 mcg/kg/day x7 p.o. plus
Prednisone 0.8 mg/kg/day x14 p.o. beginning on day 1
0.4 mg/kg/day x14 p.o.
0.2 mg/kg/day x14 p.o.

3-4 weeks after the loading dose of L-PAM when the peripheral counts are rising daily maintenance with L-PAM will be started in a dose of 50.0 mcg/kg/day p.o.

Regimen II - BCNU 150 mg/m² I.V. every 6 weeks plus
Prednisone as described under Regimen I

Regimen III - CCNU 100 mg/m² p.o. every 6 weeks plus
Prednisone as described under Regimen I

On day 154 (at the end of week 22) all patients who have not shown relapse or progressive disease will be randomized again.

Regimen A indicates that the patient should continue with initial therapy and receive no additional therapy.

Regimen B indicates that the patient should continue with his initial therapy and in addition receive Vincristine 1.0 mg/m² I.V. x1 on day 154 and every 8 weeks thereafter plus Prednisone 0.6 mg/kg/day p.o. x7 beginning on day 154 and every 8 weeks thereafter

During maintenance phase the interval between doses of BCNU or CCNU is increased from 6 to 8 weeks.

Addendum #1 dated 24 January 1975 adds

Regimen IV - L-PAM 16.0 mg/m^2 I.V. every 2 weeks for 6 weeks and then every 4 weeks plus
Prednisone as outlined under Regimen I

Addendum #2 dated 23 March 1976 provides for modification of the I.V. L-PAM dose in patients with impaired renal function.

Addendum #3 dated 29 April 1977 discontinues Regimen II and III, BCNU and CCNU.

Progress & Results: WRAMC entered six patients. One had progressive disease, one had improvement of the serum proteins but developed extensive myopathy and subsequently expired; one patient obtained a good remission, but relapsed on day 593; one patient had response but was disqualified because of erroneous maintenance, but is still in remission on day 809. The fifth patient is in response by day 475. The sixth patient was never begun on treatment by the local physician.

Conclusions: Regimen IV has a tendency for superior response.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Protocol was closed to entry of new patients in September 1977.

Task Unit No.: 1534

Title of Project: ALGB Protocol #7521. Ed. 3: A comparative study of the value of immunotherapy with MER as adjuvant to induction and two maintenance chemotherapy programs in acute myelocytic leukemia. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To determine whether early immunotherapy with MER in conjunction with a primary chemotherapeutic induction program will increase the probability of achieving complete remission.
 2. To compare remission duration and survival with respect to two types of maintenance chemotherapy, one using monthly courses of Ara-C and 6-thioguanine, the other using alternating monthly courses of Ara-C and thioguanine with vincristine, dexamethasone and Ara-C.
 3. To determine by concurrent comparative controlled trial if MER immunotherapy will prolong remission duration and increase the survival time of patients with AML receiving either of two plans of concomitant chemotherapy.
 4. To determine if the frequency of CNS leukemia and of toxicity to chemotherapy is different in patients randomly assigned to receive maintenance chemotherapy with or without vincristine and dexamethasone and with or without MER.
 5. In two programs of maintenance chemotherapy, to assess the morbidity and toxicity of MER immunotherapy.

Technical Approach: Induction Regimen is the same for all patients, consisting of:

cytosine arabinoside 100 mg/M²/day by continuous infusion from day 1 thru day 7

plus

Daunorubicin 45 mg/M²/day by rapid IV injection on days 1, 2 and 3.

If the bone marrow contains more than 5% leukemic cells, patient will receive a second course of cytosine arabinoside, this time for 5 days plus daunorubicin for 2 days.

Patients will be randomized for MER or no MER during the Induction Phase.

The Maintenance Phase consists of:

Regimen A: 5-day courses repeated every 4 weeks, consisting of:

cytosine arabinoside 100 mg/M^2 s.c.
every 12 hrs for 10 injections

plus

thioguanine 100 mg/M^2 p.o. every 12 hrs
for a total of 10 doses

plus

MER

Regimen B: cytosine arabinoside 100 mg/M^2 s.c.
every 12 hrs for a total of 10
injections

plus

thioguanine 100 mg/M^2 p.o. every 12 hrs
for a total of 10 doses

Alternate with Second five day course:

cytosine arabinoside 100 mg/M^2 s.c.
injection every 12 hrs, total of 10
injections on days 1 thru 5

plus

vincristine 2 mg/M^2 , 2 mg max., on
day 1 of this course

plus

dexamethasone 8 mg/M^2 , not to exceed
16 mg p.o. in 3 divided doses daily
on day 1 thru 5

plus

intra-dermal MER

Regimen C: 5-day course repeated every 4 weeks
cytosine arabinoside 100 mg/M^2 s.c.
every 12 hrs, total of 10 injections

plus

thioguanine 100 mg/M^2 p.o. every 12 hrs
for a total of 10 doses

In all 3 regimens, the 3rd, 7th, 11th and 15th courses are
substituted for cytosine arabinoside 100 mg/M^2 s.c. every
12 hours, total of 10 injections

plus

dexamethasone 15 mg/M^2 /day by rapid IV injection on days
1 and 2.

Progress & Results: WRAMC has entered 28 patients. Twelve patients obtained a complete remission, 4 of whom relapsed from 114 to 250 days; 4 patients had a partial remission, 3 of whom relapsed, and one was disqualified. Twelve patients did not respond and had progressive disease and died. Eight patients remain in complete remission from 271 to 875 days.

Conclusions: It seems that MER in the induction phase may benefit patients who have negative skin tests prior to treatment. It is too early for evaluation of duration of response.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim. Protocol was closed to patient entry on 10 June 1977.

Work Unit No.: 1535

Title of Project: ALGB Protocol #7581 - Add. #1: Long term surgical adjuvant systemic chemotherapy with or without adjuvant immunotherapy in mammary carcinoma. A comparative study of cytoxan, vincristine, methotrexate, 5-fluorouracil, prednisone vs. cytoxan, methotrexate, 5-fluorouracil vs. cytoxan, methotrexate, 5-fluorouracil, MER. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. It is the specific aim of this study to ascertain if therapy with 3 active agents plus nonspecific immunostimulation is superior to the 3 active agents given alone, or given in combination with vincristine and prednisone. The criteria for assessment will be the disease free interval of breast cancer patients with 4 or more positive axillary nodes discovered at mastectomy. A corollary comparison to the historical information in a patient group similarly staged and operated when followed by observation alone or by 3 active agent therapy in Milan will be utilized for an additional comparison.
 2. The duration of the disease free interval in each treatment will be evaluated for its impact upon survival, as well as serving the principle measure of therapeutic effect.
 3. Patient tolerance to the therapeutic regimens will be evaluated.
 4. The site of first recurrence of disease will be evaluated to determine any differential action of the regimens.
 5. An attempt will be made to determine if patient age, primary lesion size, or the utilization of postoperative radiotherapy influenced the recurrence or survival rates, as well as the location of the site of first recurrence.

Technical Approach: Induction Phase Treatment Schedules

Regimen I: cytoxan 80 mg/M²/day orally for 42 consecutive days
plus
methotrexate 40 mg/M²/week IV for 6 consecutive weeks
EXCEPT patients 60 years of age are to receive 30 mg/M²/week IV

plus
 5-FU 500 mg/M²/week IV for 6 consecutive weeks
 plus
 vincristine 1.0 mg/M²/week IV for 6 consecutive weeks (max. dose 1.5 mg per dose)
 plus
 prednisone 40 mg/M²/day orally daily in 3 divided doses for 21 consecutive days followed by half dose for 2 consecutive days; followed by quarter dose for 2 consecutive days; followed by one-eighth dose for 2 days, then discontinue

Treatment will begin no sooner than two weeks and not later than four weeks following mastectomy in those patients not receiving postoperative radiotherapy. If postoperative radiotherapy is given, chemotherapy will begin no sooner than 4 weeks and not later than 8 weeks following completion of radiotherapy (and not later than 16 weeks from mastectomy)

Regimen II: cytoxan 80 mg/M²/day orally for 42 consecutive days
 plus
 Methotrexate 40 mg/M²/week IV for 6 consecutive weeks, EXCEPT patients 60 years or older are to receive 30 mg/M²/week IV
 plus
 5-FU 500 mg/M²/week IV for 6 consecutive weeks

Regimen III: cytoxan 80 mg/M²/day orally for 42 consecutive days
 plus
 methotrexate 40 mg/M²/week IV for 6 consecutive weeks EXCEPT patients 60 years or older are to receive 30 mg/M²/week IV
 plus
 5-FU 500 mg/M²/week IV for 6 consecutive weeks
 plus
 MER 200 ug intradermally in each of 5 sites (total 1 mg) at weeks 1, 3 and 5

MER should be swirled in the vial and repeatedly tilted in the tuberculin syringe to assure its homogeneous suspension. Injection sites should be chosen to drain into different node groups. Do not inject lymphadenomatous arm.

Maintenance Phase Treatment Schedules for First Year of Maintenance

Regimen I: cytoxan 100 mg/M²/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M² IV day 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M²
plus
5-FU 500 mg/M² IV day 1 and day 8 of each cycle
plus
vincristine 1.0 mg/M² IV day 1 and day 8 of each cycle (max. dose 1.5 mg/dose)
plus
prednisone 40 mg/M²/day orally days 1-14 of each cycle DO NOT TAPER

Each cycle of therapy is 28 days in length and recycle begins on day 29. This regimen should be given for 10 cycles, after which patients enter the Second Year of Maintenance (see below)

Regimen II: cytoxan 100 mg/M²/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M² IV days 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M²
plus
5-FU 500 mg/M² IV day 1 and day 8 of each cycle

Each cycle of therapy is 28 days in length and recycle begins on day 29. This regimen should be given for 10 cycles, after which patients enter the Second Year of Maintenance

Regimen III: cytoxan 100 mg/M²/day orally days
1-14 of each cycle
plus
methotrexate 40 mg/M² IV days 1 and
day 8 of each cycle EXCEPT patients
60 years or older are to receive
30 mg/M²
plus
5-FU 500 mg/M² IV day 1 and day 8 of
each cycle
plus
MER 200 ug intradermally in each of
5 sites (total 1 mg) on day 8 of
each cycle.

Each cycle of therapy is 28 days in length and
recycle begins on day 29. This regimen should be
given for 10 cycles, after which patients enter
the Second Year of Maintenance.

Maintenance Phase Treatment Schedule for Second Year of Maintenance

At the scheduled time for the 11th cycle of
maintenance therapy, patients in all 3 regimens
will begin a uniform treatment schedule.
Vincristine and prednisone are dropped from
regimen I; MER is dropped from regimen III and
the length of a treatment cycle is increased to
56 days.

In the second year of maintenance, all patients
will receive:

cytoxan 100 mg/M²/day orally days 1-14
of each cycle
plus
methotrexate 40 mg/M² IV on day 1 and
day 8 of each cycle EXCEPT patients
60 years or older are to receive
30 mg/M²
plus
5-FU 500 mg/M² IV on day 1 and day 8 of
each cycle

Each cycle of therapy is 56 days in length and
recycle begins on day 57. Treatment should continue
for 6 cycles, after which, all treatment is dis-
continued and the patient should be observed
indefinitely at 3 month intervals without further
therapy.

Progress & Results: WRAMC has entered 24 patients, one of whom relapsed on day 240 and one on day 832. One patients was not eligible. All other patients remain in complete remission from 50 to 977 days.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1536

Title of Project: ALGB Protocol 7531 - Add. 0: Treatment of Chronic Myelocytic Leukemia with the Aim of the Prevention of Myeloblastic Transformation. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine whether longer courses of CCNU and Ara-C, begun at time of diagnosis and without Busulfan, can postpone or prevent myeloblastic transformation.

Technical Approach:

Regimen I - Busulfan 4 mg/m^2 daily for induction and maintenance

Regimen II - CCNU 35 mg/m^2 orally every 6 weeks plus
Ara-C 50 mg/m^2 s.c. q 12 hours on days 1-5 of each
6-week cycle

Progress & Results: WRAMC has entered three patients. One had progressive disease on day 84, one patient refused treatment after he was randomized and the third patient was disqualified because of prior treatment.

ALGB has entered 92 patients, 81 of whom were evaluable in June 1977. Control of the disease with CCNU and Ara-C is more difficult to obtain. The study has not progressed long enough to determine any difference in blastic transformation in the two treatment regimens, however sufficient patients have been entered and therefore the study was discontinued on 16 June 1977.

Conclusions: CML is easier to control with busulfan than with the combination of CCNU and Ara-C. Any difference in the development of blastic crisis cannot be evaluated at the present time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Terminated

Work Unit No.: 1537

Title of Project: ALGB Protocol #7551, Add. #0: Combination chemotherapy and radiotherapy for stage IV Hodgkin's disease, no prior treatment.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To compare the response rates and remission durations observed with 6 or 12 monthly cycles of chemotherapy.
 2. To determine the effectiveness of a combined approach by radiotherapy and multiple drug chemotherapy in the control of Stage IV Hodgkin's Disease as compared to multiple drug chemotherapy alone.
 3. To explore whether early reduction of bulk disease by radiotherapy is beneficial in controlling the disease.
 4. To explore the ability of radiotherapy to eradicate residual microscopic disease in patients with apparent complete remission after a full course of multiple drug chemotherapy.
 5. To explore the ability of radiotherapy to eradicate disease in patients with apparent partial remission after a full course of multiple drug chemotherapy.

Technical Approach: Regimen I: CCNU 75 mg/M² p.o. day 1
vinblastine 4 mg/M² IV day 1 and 8
procarbazine 100 mg/M² p.o. day 1
thru 14
prednisone 40 mg/M² p.o. day 1 thru 14

Prednisone is given on course 1 and 4 only.

After each course of treatment, there is a 2 week rest period. This treatment is given for a total of six courses.

Regimen II: Is the same as Regimen I, but the therapy should continue for a total of twelve courses.

The prednisone is given on courses 1, 4, 7 and 10 only.

Regimen III: Consists of six months of chemotherapy, as outlined in Regimen I, plus radiation therapy.

Regimen IV: Is the same chemotherapy as outlined in Regimen I, to be given for three courses, after which radiation therapy will be administered. Four weeks after the completion of radiation, another three courses of chemotherapy will be administered.

The radiation therapy will consist of 2500 rads to be given in 4 weeks to areas of gross disease known to exist prior to the start of chemotherapy.

All patients will be placed on maintenance therapy which will consist of:

chlorambucil 6 mg/M² given daily for a total of 3 years, or until progressive disease.

Progress & Results: WRAMC has entered six patients. Three are in a continued complete remission from 155 to 366 days. One had a partial remission on day 258 and subsequently expired and another patient continues in partial remission on day 355. One patient is too early for evaluation.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1538

Title of Project: CALGB Protocol #7552. Add. #2: Combination chemotherapy and immunotherapy for previously treated Stage III and IV Hodgkin's Disease.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To compare remission rates and the remission duration of two, four drug chemotherapy regimens employing completely different agents in previously treated patients with Stage IV Hodgkin's Disease.
 2. To compare the response rates and remission durations of the repetitive use of the four drug combination regimens with alternating cycles of the two entirely different regimens, thus exposing the patient to eight drugs.
 3. To compare the efficacy of chemotherapy and chemo-immunotherapy with respect to response rates, remission durations, and toxicity.
 4. To assess immunological tests of delayed MER hypersensitivity as prognostic indices, and to compare the effects of different combined chemotherapies and of immunotherapy upon them.

Technical Approach: Regimen IA or CCNU 75 mg/M² p.o. on day 1
 Regimen IB plus
 vinblastine 4 mg/M² IV on days
 1 and 8
 plus
 procarbazine 100 mg/M² p.o. on
 days 1 thru 14
 plus
 prednisone 40 mg/M² p.o. on days
 1 thru 14

Prednisone is included in courses 1, 4, 7, and 10 only.

Patients randomized to Regimen IA will receive in addition to this chemotherapy, immunotherapy with MER 200 ug intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IB will receive chemotherapy only.

Regimen IIA 500 µg/m² I.V. on days 1
or Regimen IIB and 8
plus
adriamycin 50 mg/m² I.V. on day 1
(max. total dose 550 mg/m²)
plus
vincristine 1.4 mg/m² I.V. on days 1
and 8
plus
streptozotocin 1500 mg/m² I.V. on
days 1 and 8

After each 2 week treatment period, there will be a 2 week rest period. Patient will receive a total of 12 courses.

Patients randomized to Regimen IIA will receive in addition to this chemotherapy, immunotherapy with MER, 200 µg intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IIB will receive Regimen II chemotherapy only.

Regimen IIIA Will consist of 12 courses of induction
or Regimen IIIB therapy. Each course will consist of 2 weeks of chemotherapy, and a course will be given every 4 weeks.

Regimen III will be alternate courses of Regimen I and Regimen II chemotherapy.

Patients randomized to Regimen IIIA will receive in addition to this chemotherapy, immunotherapy with MER, 200 µg intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IIIB will receive Regimen III chemotherapy only.

Maintenance Therapy: At the end of 12 courses of induction therapy, all patients who are in complete or partial remission status will receive: chlorambucil 6 mg/m²/day

Addendum 2 : Decrease in dose of Streptozotocin.

Progress & Results: WRAMC entered four patients, all of whom obtained a complete remission. Three remain in remission from 630 to 915 days. One patient developed a preleukemic state on day 284.

Conclusions: Presently there is no difference in response rate between regimens with and without immunotherapy. However, there is a tendency towards prolonged remission.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No: 1539

Title of Project: CALGB Protocol 7541 - Add. 0: Combination Chemotherapy and Immunotherapy in Previously Untreated Stage III and IV Neuroblastoma. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To evaluate the role of triple drug (vincristine, cyclophosphamide, adriamycin) combination chemotherapy in previously untreated Stage III and IV neuroblastoma.
 2. To evaluate the immunological responsiveness of patients with disseminated neuroblastoma, both prior to and during therapy.
 3. To evaluate the role of an agent (MER) thought capable of stimulating immunological responsiveness both in terms of the patient's immunological reactivity (to skin tests) and in terms of possible contribution to prolongation of median survival.

Technical Approach:

- Regimen I - Vincristine 1.5 mg/m^2 I.V. on days 1, 8, 29, 36, 57, 64, 85, 92 and for a similar schedule (two weeks out of every four) for a total of one year plus
Cyclophosphamide 500 mg/m^2 on days 1, 57 and every two months thereafter for one year, and $1,000 \text{ mg/m}^2$ on days 29, 85 and every two months thereafter for one year plus
Adriamycin $25 \text{ mg/m}^2/\text{day} \times 3$ I.V. beginning on days 1, 57 and every two months thereafter
- Regimen II - Vincristine 1.5 mg/m^2 I.V. on days 1, 8, 29, 36, 57, 64, 85, 92, and for a similar schedule (two weeks out of every four) for a total of one year plus
Cyclophosphamide 500 mg/m^2 on days 1, 57 and every two months thereafter for one year, and $1,000 \text{ mg/m}^2$ on days 29, 85 and every two months thereafter for one year plus
Adriamycin $25 \text{ mg/m}^2/\text{day} \times 3$ I.V. beginning on days 1, 57 and every two months thereafter plus
MER 200 ug in each of 5 sites (total 1 mg) intradermally on days 8, 36, 64 and every fourth week thereafter.

Treatment Procedures:

1. Laparotomy and tumor resection will be performed as appropriate.
2. Patients with Stage III disease will have scheduled radiotherapy beginning 5 weeks after the first course of chemotherapy, providing hematologic thresholds are satisfied
3. Patients with Stage IV disease will have radiotherapy used electively, beginning 5 weeks after the first dose of chemotherapy, providing hematologic thresholds are satisfied, unless emergency indicated appearance beforehand. The radiation therapy will be given in 180-200 rad fractions at a rate of one fraction per day for a total schedule of five fractions per week.

Progress & Results: Five patients have been entered at WRAMC. One patient was ineligible because of prior treatment. One patient has had considerable regression in tumor size and continues in a stable state on day 504. One patient died on day 89; one has stable disease on day 70 and one is too early for evaluation.

Conclusions: Both regimens demonstrate responses. It is too early for any comparison.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1541

Title of Project: CALGB Protocol #7542. Add. #0: Protocol for the treatment of Non-Hodgkin's lymphomas in children. Methotrexate, Vincristine, Dexamethasone, Cyclophosphamide, 6-Mercaptopurine plus radiation therapy to involved areas. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

- Objectives:
1. To develop a combined radiotherapy/chemotherapy regimen which will increase the survival and cure rate in children with non-Hodgkin's lymphoma not previously treated.
 2. To determine the efficacy of the addition of daily oral 6-MP and weekly oral MTX to standard lymphoma-type maintenance with high dose intermittent Cyclophosphamide and Vincristine-steroid reinforcements in Stage I, II and III disease.
 3. To test the efficacy of high dose Methotrexate (500 mg/ M^2) in a maintenance program for patients with Stage IV disease.

Technical Approach: Stages I, II and III Induction Treatment will consist of:
vincristine 2 mg/ M^2 IV x 4 doses given on days 1, 8, 15 and 22
plus
dexamethasone 6 mg/ M^2 p.o. daily x 4 weeks and then taper
plus
methotrexate 12 mg/ M^2 IT given on days 1, 8, 15 and 22
Radiation therapy will begin on day 15.

Maintenance:

Regimen I: cyclophosphamide 500 mg/ M^2 IV push x 1 beginning on day 36 of study and every 4 weeks thereafter
plus
vincristine 2 mg/ M^2 IV push x 1 beginning on day 36 and every 4 weeks thereafter
plus

dexamethasone 6 mg/M² p.o. daily x
7 days every 4 weeks beginning on
day 64 of study
plus
methotrexate 15 mg/M² p.o. once weekly
plus
6-MP 75 mg/M² p.o. daily

Regimen II: cyclophosphamide 1,000 mg/M² IV push
x 1 beginning on day 36 and every
4 weeks thereafter
plus
vincristine 2 mg/M² IV push x 1
beginning on day 36 and every 4 weeks
thereafter
plus
dexamethasone 6 mg/M² p.o. daily x
7 days every 4 weeks beginning on
day 64

Treatment of Stage IV Disease - Induction

All Stage IV patients will receive the same
therapy, consisting of:

vincristine 2 mg/M²/week IV x 4
doses given on days 1, 8, 15 and 22
plus
dexamethasone 6 mg/M² p.o. daily x
4 weeks and then taper
plus
methotrexate 12 mg/M² IT given on
days 1, 8, 15 and 22

Radiation therapy will begin on day 15.

Intensification

Regimen III: vincristine 2 mg/M²/week IV x 3 doses
given on days 36, 57 and 78 of study
plus
dexamethasone 6 mg/M² p.o. daily x 1
week beginning on days 57 and 78
plus
methotrexate 12 mg/M² IT given on
days 36, 57 and 78. IT MTX should be
given between 1/2 and 2 hours after
the start of the high dose MTX
(500 mg/M²)
plus

methotrexate 500 mg/M² 1/3 IV push
and 2/3 IV drip over 24 hours
given on days 36, 57 and 78
plus
leucovorin twenty-four hours after
completion of each course of MTX
(500 mg/M²), leucovorin will be
given at 12 mg/M² IV or IM once
only as "rescue"

Maintenance therapy will begin on day 85 after the
completion of the Intensification

Regimen IV: cyclophosphamide 500 mg/M² IV push
x 1 beginning on day 36 of study and
every 4 weeks thereafter
plus
vincristine 2 mg/M² IV push x 1
beginning on day 36 and every 4 weeks
thereafter
plus
dexamethasone 6 mg/M² p.o. daily x 7
days every 4 weeks beginning on day
64
plus
methotrexate 15 mg/M² p.o. once weekly
plus
6-MP 75 mg/M² p.o. daily
plus
IT Methotrexate 12 mg/M² IT given on
days 36, 43 and 50

The radiation dose is 3500 rads in 3-1/2 to 4 weeks,
given in 180 to 200 rad fractions.

Progress & Results: WRAMC entered three patients. One had improvement,
but rapidly recurrent disease and subsequently died;
the second patient has no evidence of disease on day
572 and the third patient had a complete remission
but died on day 398 from a pulmonary process of un-
known etiology.

Conclusions: These are active regimens, however no comparison can be
made at the present time.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publicatons: None

Type of Report: Entry of new patients on protocol was closed in November 1977. Final

Work Unit No.: 1542

Title of project: CALB Protocol 7583. Adjuvant Chemotherapy in Osteogenic Sarcoma, Adriamycin vs. Sequential Adriamycin, High Dose Methotrexate - Citrovorum Factor vs. Sequential Adriamycin - Cyclophosphamide. Addendum 1, dated 17 June 1976, entries to Regimen III were temporarily suspended pending further pilot observation.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

- Objectives:
1. To determine the relative duration of disease-free interval and survival for patients treated with six courses of adriamycin alone, or sequential adriamycin and high dose methotrexate, followed with citrovorum factor rescue, or sequential adriamycin and high dose cyclophosphamide after radical operation of either primary lesion, or complete resection of pulmonary metastasis or osteogenic sarcoma.
 2. To determine the patient's tolerance to these different therapeutic regimens.

Technical Approach:

Regimen I - Adriamycin 30 mg/m^2 daily for 3 days I.V. to be repeated every 4 weeks for 6 courses. The treatment will be no sooner than 4 days and not later than 4 following operation.

Regimen II: Day 1 to 3, adriamycin 30 mg/m^2 I.V. daily
Day 28 to 30, adriamycin 30 mg/m^2 I.V. daily
Day 56, high dose methotrexate 200 mg/kg body weight I.V. infusion for 6 hours. Two hours after completion of the high dose MTX infusion, administer citrovorum factor 12 mg I.M. every 6 hours for 12 doses.
Day 77, high dose methotrexate 200 mg/kg I.V. infusion for 6 hours. Two hours after completion of infusion, administer citrovorum factor 12 mg I.M. every 6 hours for 12 doses.
Day 105, repeat the above adriamycin, high dose MTX plus citrovorum factor sequence at the same dose and interval for a total of 6 courses for each agent.

Regimen III - Day 1 to 3, adriamycin 30 mg/m² I.V. daily
Day 23 to 30, adriamycin 30 mg/m² I.V. daily
Day 56, cyclophosphamide 25 mg/kg I.V. every other day
for 5 doses over a 10-day period
Day 98, repeat the above adriamycin, cyclophosphamide
sequence for a total of 6 courses for adriamycin and
3 courses for cyclophosphamide.

Progress & Results: WRAMC entered seven patients. Treatment had to be stopped in one patient on day 73 because of toxicity. One patient relapsed on day 134. The remaining five patients are free of disease from 148 to 435 days.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1543

Title of Project: CALGB Protocol #7651. A Phase III Study.
Combination chemotherapy of Stage III and IV
lymphocytic lymphoma (lymphosarcoma) in adults
with or without radiotherapy consolidation.
Induction: Vincristine, Streptonigrin, Prednisone
Maintenance: Cyclophosphamide. Addendum 1.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To confirm the improvement of remission induction in advanced lymphocytic lymphoma by adding streptonigrin to vincristine and prednisone in this phase.
 2. To explore the therapeutic potential of radiation therapy in advanced lymphocytic lymphoma following an initial remission induction with combination chemotherapy by comparing identical chemotherapy maintenance arms, one of which adds radiotherapy to initially involved areas.

Technical Approach: Induction vincristine 1 mg/M^2 IV on days 1, 8, 15, 22, 29 and 36
plus
streptonigrin 1 mg/M^2 p.o. spaced over 1 hr on days 1, 8, 15, 22, 29 and 36
plus
prednisone 40 mg/M^2 p.o. daily in one dose for 42 days, then tapered by halving the dose every 2 days until the patient is receiving $5 \text{ mg/M}^2/\text{day}$, after 3 days of which it should be stopped

Consolidation and Maintenance Regimens for Patients Who Have Obtained at Least a Partial Remission

Regimen I: Maintenance should begin immediately with:
cyclophosphamide 1 gm/M^2 IV
plus
vincristine 1 mg/M^2 (max. 2 mg) IV
plus
prednisone 40 mg/M^2 p.o. daily (in one dose) x 7 days

Regimen II: Patients will receive an initial consolidation phase with chemotherapy and radiotherapy to the areas initially involved at the time of entry to the study, to be followed by maintenance chemotherapy. The map of disease distribution prepared on entry will be used to define the sites of radiotherapy.

Radiation therapy will be given in a dose of 3500 to 4000 rads in 4 weeks to the sites of involvement. The daily dose will vary from 180 to 200 rads.

Progress & Results: WRAMC entered twelve patients; four obtained complete remission, and are in remission from 286 to 793 days; two had a partial remission; one relapsed on day 453; one remains in remission on day 78. One could not complete the treatment because of toxicity and two patients were disqualified. Three patients had progressive disease.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1544

Title of Project: CALGB Protocol #7652. A Phase III Study. Combination chemotherapy of Stage III and IV histiocytic lymphoma (reticulum cell sarcoma) in adults with or without radiotherapy or Adriamycin consolidation.
Induction: Vincristine, Streptonigrin, Prednisone
Consolidation: Adriamycin
Maintenance: Cyclophosphamide
Addendum 1

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To confirm the improvement of remission induction in advanced histiocytic lymphoma by adding streptonigrin to vincristine and prednisone in this phase.
 2. To explore the therapeutic potential of radiation therapy in advanced histiocytic lymphoma following initial remission induction with combination chemotherapy.
 3. To evaluate the benefits of a consolidation phase with Adriamycin.

Technical Approach: The induction program for all patients will consist of:

vincristine 1 mg/M^2 IV on days 1, 8, 15, 22, 29 and 36
plus
streptonigrin 1 mg/M^2 p.o. spaced over 1 hour on days 1, 8, 15, 22, 29 and 36
plus
prednisone 40 mg/M^2 p.o. daily in one dose for 42 days, then tapered by halving the dose every 2 days until the patient is receiving 5 mg/M^2 per day, after 3 days of which it should be stopped.

Consolidation and Maintenance will be begun on all patients who have obtained at least a partial remission after 6 weeks of induction.

Regimen I: Patients are begun on maintenance chemotherapy immediately, consisting of cyclophosphamide 1 gm/M^2 IV plus vincristine 1 mg/M^2 plus prednisone 40 mg/M^2 p.o. daily for 7 days.

The first 4 courses are to be given at 3 week intervals, after the 4th course continued every 4 weeks.

Regimen II: Patients will receive consolidation phase with 3 courses of adriamycin, vincristine and prednisone after completion of the 6 week induction phase. Consolidation phase consists of:
adriamycin 60 mg/M^2 IV q 3 weeks x 3
plus
vincristine 1 mg/M^2 IV q 3 weeks x 3
plus
prednisone $40 \text{ mg/M}^2/\text{day}$ p.o. x 7 days q 3 weeks.

Maintenance phase is to be started 3 weeks after the last consolidation course, and will consist of: cyclophosphamide, vincristine and prednisone every 4 weeks, as outlined under Regimen I.

Regimen III: The patient is to receive an interim consolidation phase with chemotherapy and radiotherapy to the areas initially involved at the time of entry into the study, to be followed by maintenance chemotherapy.

The radiotherapy shall be delivered to all areas with known initial involvement which were greater than 2 cm in diameter at time of entry into study. If the total aggregate field area is under 300 sq cm the dose will be 4000 rads in 4-5 weeks. If the fields required measure greater than 300 sq cm, the dose will be 3000 rads in 4-5 weeks. This dose will be delivered in 180 to 200 rad fractions daily.

Progress & Results: WRAMC entered three patients. Two had no response and went off study. One remains without evidence of disease on day 1007.

The study was closed to entry of new patients on 16 June 1977.

Conclusions: Although responses are adequate newer treatments have become available, and therefore the study was closed.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1546

Title of Project: ONCOB Protocol 7611, Add. 0: Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years with Vincristine (NSC 67574), Prednisone (NSC 10023), Methotrexate (NSC 740), L-Asparaginase (NSC 109229), and 6-Mercaptopurine (NSC 755), plus Cranial Irradiation. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

- Objectives:
1. To test whether the substitution of high dose methotrexate with leucovorin rescue for cranial irradiation decreases the frequency of occurrence of CNS leukemia.
 2. To test whether remission consolidation with 3 courses of high dose methotrexate with leucovorin rescue prolongs complete remission duration.

Technical Approach:

Induction Phase: Vincristine 2 mg/m^2 I.V. $\times 4$ on days 1, 8, 15 and 22 (maximum dose 2 mg)
Prednisone $40 \text{ mg/m}^2/\text{day}$ p.o. daily $\times 4$ weeks and then tapered over 10 days
Methotrexate 12 mg/m^2 IT $\times 3$ on days 15, 22, 29 (maximum dose 15 mg)
L-Asparaginase 1000 iu/kg/day I.V. on days 29 thru 38

After completion of the L-asparaginase treatment patients will be randomized between:

- Regimen A - High dose Methotrexate 500 mg/m^2 over 24 hours on days 43, 64 and 85
Leucovorin 24 hours after completion of each course of methotrexate at a dose of 12 mg/m^2 plus
Methotrexate 12 mg/m^2 IT $\times 3$ doses on days 43, 64 and 85
Vincristine 2 mg/m^2 I.V. on day 78
Prednisone 40 mg/m^2 p.o daily $\times 7$ days beginning on day 78
- Regimen B - Methotrexate 12 mg/m^2 IT $\times 3$ on days 43, 50 and 57 (maximum dose of IT MTX 15 mg)
Cranial Irradiation 2400 rads over a period of 16 days beginning on day 43

34
Upon completion of this so-called secondary phase of treatment patients will be placed on

Maintenance Phase: 6-Mercaptopurine 90 mg/m^2 /day p.o.
Methotrexate 15 mg/m^2 /week p.o. on the first day of each week, plus
Reinduction courses of vincristine plus prednisone at 6, 12, 16, 20 and 24 weeks. Beginning 28 weeks after L-asparaginase two doses of vincristine one week apart and 14 days of prednisone will be given every 12 weeks until relapse.

Progress & Results: WRAMC has entered three patients. One patient went off study on day 42 because local physician referred to give the maintenance drugs. Two patients obtained a complete remission, one remains in remission on day 112 and one relapsed on day 219.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Task Unit No.: 1547

Title of Project: CALGB Protocol 7682, Add. 0: Combination Chemotherapy or Chemoprevention for Metastatic Recurrent or Inoperable Carcinoma of the Breast. Three Treatment Regimens: Cyclophosphamide (NSC 26271), Adriamycin (NSC 123127), 5-Fluorouracil (NSC 19893) vs. Cyclophosphamide, Adriamycin, 5-Fluorouracil, Vincristine (NSC 67574), Prednisone (NSC 10023) vs. Cyclophosphamide, Methotrexate (NSC 740), 5-Fluorouracil, All with or without MER (NSC 143769). A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To compare the remission induction frequency and duration of the CAF and the CMF combination individually with the five-drug combination, CAFVP, which appears to be the best combination program in CALGB study 7482.
 2. To test whether the addition of MER to each of the three combinations increases the remission induction frequency or prolongs the remission duration, or both.
 3. To determine whether MER alters the tolerance of normal tissues to these combination chemotherapeutic programs.
 4. To establish the initial immunocompetence of patients with metastatic breast cancer as determined by skin testing; to assess whether the administration of MER alters that initial status, and to test whether any such changes are associated with a prolongation of disease control.
 5. To determine the influence of metastatic disease patterns at time of first recurrence following mastectomy and at onset of protocol upon the remission induction frequency and remission duration.

Technical Approach: Prior to randomization for treatment patients will be stratified according to dominance of metastatic area, visceral osseous soft tissue which develop either less than one year from diagnosis or equal to or greater than one year from diagnosis.

Regimen IA - Cyclophosphamide $100 \text{ mg/m}^2/\text{day}$ p.o. days 1-14
Methotrexate 40 mg/m^2 I.V. days 1 and 8; for patients
> 60 years 30 mg/m^2 I.V. days 1 and 8
5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8

This cycle is to be repeated every 28 days.

Regimen IB - Same as Regimen IA plus MMR.

Regimen IIA - Cyclophosphamide 100 mg/m²/day p.o. days 1-14
Adriamycin 25 mg/m² I.V. days 1 and 8 to a total dose
of 450 mg/m²
5-Fluorouracil 500 mg/m² I.V. days 1 and 8

This cycle is to be repeated every 28 days.

Regimen IIE - Same as Regimen IIA plus MMR.

Regimen IIIA - Cyclophosphamide 100 mg/m² p.o. days 1-14
Adriamycin 25 mg/m² I.V. days 1 and 8 to a total dose
of 450 mg/m²
5-Fluorouracil 500 mg/m² I.V. days 1 and 8
Vincristine 1.0 mg/m² I.V. days 1 and 8 with maximum
dose of 2 mg
Prednisone 40 mg/m²/day p.o. days 1-14

Each cycle is to be repeated every 28 days.

Regimen IIIB - Same as Regimen IIIA plus MMR.

Progress & Results: WRAMC has entered seven patients on study. One had progressive disease on day 179; one on day 286 and one on day 136. Two patients remain in complete remission on day 557 and 368. One had a partial remission and relapsed on day 409. One patient expired on day 130.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1548

Title of Project: CALB Protocol 7681, Add. 0: Investigation of the Effects of Adriamycin with and without Alled MER in Soft Tissue Sarcomas. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To compare the effectiveness of adriamycin alone and adriamycin together with MER in the induction of remission in inoperable soft tissue sarcomas.
 2. To compare the effectiveness of single monthly doses and three consecutive daily doses/month of adriamycin.
 3. To determine whether the addition of MER to adriamycin treatment affects the duration of remission in patients with inoperable soft tissue sarcomas.

Technical Approach:

Regimen IA - Adriamycin 75 mg/m^2 I.V. every four weeks to a maximum dose of 550 mg/m^2

Regimen IB - Adriamycin plus MER 1 mg intracutaneously on day 1 and 8 to be repeated every four weeks

Regimen IIA - Adriamycin 25 mg/m^2 on days 1, 2 and 3, to be repeated every four weeks to a maximum dose of 550 mg/m^2

Regimen IIB - Adriamycin plus MER 1 mg intracutaneously on day 1 and 8 every four weeks.

Patients who are in a remission or who have no evidence of progressive disease and who have received the maximum dose of 550 mg/m^2 of adriamycin will be placed on cyclophosphamide 750 mg/m^2 day 1 only, vincristine 1.5 mg/m^2 I.V. daily day 1 and weekly thereafter for a total of 8 doses, plus DTIC 250 mg/m^2 I.V. days 1 thru 5. Cyclophosphamide and DTIC will be repeated every four weeks. Patients who are on MER should be continued on MER.

Progress & Results: WRAMC entered three patients on study. Two had progressive disease and expired. The third patient is too early for evaluation.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1551

Title of Project: CALGB Protocol 7612, Add. 1: Therapy of Acute Lymphocytic Leukemia in Adults: A Comparison of Vincristine, Prednisone and L-Asparaginase with or without Daunorubicin for Induction with Central Nervous System Prophylaxis with Radiotherapy and Intrathecal Methotrexate and Maintenance with 6-Mercaptopurine and Methotrexate with or without Immunotherapy with MER. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To test whether the addition of daunorubicin to vincristine and prednisone followed by L-asparaginase will increase the frequency of complete remission in adults with acute lymphocytic leukemia.
 2. To test whether the addition of immunotherapy in the form of MER to maintenance therapy prolongs remission durations.
 3. To assess the efficacy of employing CNS prophylaxis with intrathecal methotrexate plus cranial irradiation immediately following remission induction.

Technical Approach:

Regimen I - Vincristine 2 mg I.V. once weekly x3 plus
Prednisone 40 mg/m² p.o. daily for 21 days plus
L-asparaginase 500 i.u./kg M.V. daily for 10 days
beginning on day 22

Regimen II - Vincristine 2 mg I.V. weekly x3
Prednisone 40 mg/m² p.o. daily for 21 days
Daunorubicin 45 mg/m² I.V. daily for 3 days followed by
L-asparaginase 500 i.u./kg I.V. daily for 10 days
starting on day 22
Prednisone will be tapered over 10 days

Progress & Results: WRAMC entered six patients. Five of whom obtained complete remissions. One refused maintenance. One relapsed on day 414, one patient died on day 40 and the other three remain in remission from 61 to 141 days.

Conclusions: Too early

34
Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1552

Title of Project: CALGB Protocol 7632, Add. 0: Chemotherapy in
Indolent Chronic Lymphocytic Leukemia. A Phase
III Study. (Chlorambucil (Leukeran) NSC 3088)

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To test whether the administration of intermittent chlorambucil in patients with indolent CLL of categories 2 and 3 delays or possibly prevents the development of aggressive CLL in comparison to a no treatment group.
2. To test whether the administration of intermittent chlorambucil prolongs survival with the disease in comparison to a no treatment group.

Technical Approach: Patients will be kept for 12 weeks in an observation period. Afterwards they will be randomized to Regimen I, which is no treatment, or Regimen II, which is treatment with intermittent chlorambucil 0.5 mg/kg p.o. every 28 days.

Progress & Results: WRAMC has entered no patients.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1553

Title of Project: CALGB Protocol 7661, Add. 0: Multiple Myeloma Resistant to Melphalan Treated with Cyclophosphamide (NSC 26271), Adriamycin (NSC 123127), BCNU (NSC 402962), and Prednisone (NSC 10023). A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

- Objectives:
1. To test whether patients previously treated with melphalan but with recurrent disease will respond to the combination of adriamycin, cyclophosphamide and prednisone.
 2. To test whether patients previously treated with melphalan but with recurrent active disease will respond to the combination of adriamycin, BCNU and prednisone.

Technical Approach:

Regimen I - Adriamycin 30 mg/m² I.V. on day 1
Cyclophosphamide 400 mg/m² I.V. on day 1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses beginning on day 1)

Then, every 3 weeks:
Adriamycin 30 mg/m² I.V. x1
Cyclophosphamide 400 mg/m² I.V. x1
Prednisone 0.6 mg/kg/day x7 (in 3 equally divided doses)

Regimen II - Adriamycin 30 mg/m² I.V. on day 1
BCNU 75 mg/m² I.V. on day 1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses beginning on day 1)

Then every 3 weeks:
Adriamycin 30 mg/m² I.V. x1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses)

Then every 6 weeks:
BCNU 75 mg/m² I.V. x1

Progress & Results: WRAMC entered one patient who had progressive disease on day 172.

Conclusions: In both regimens a similar number of worthwhile responses were observed.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Protocol was closed to entry of new patients in June 1978.
This is the final report.

Work Unit No.: 1554

Title of Project: CALGB Protocol #7691: Comparison of Involved Field Radiotherapy with Involved Field Radiotherapy with Adjuvant MOPP Chemotherapy and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkin's Disease in Children.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To compare the effectiveness of IF radiotherapy, IF radiotherapy followed by MOPP chemotherapy, and EF radiotherapy, in treating laparotomy confirmed Stage I and II Hodgkin's Disease in children in terms of: a) duration of disease-free interval following completion of initial therapy, b) the type and extent of disease extensions following initial therapy, and c) survival.

To determine the retrievability of new disease following primary therapy for each of the three regimens, using specified retrieval plans.

To determine the effect of specific histology on results of primary and retrieval therapy for each of the three regimens.

To determine the comparative effects of the three treatment regimens with respect to:

- a) Linear growth, bi-acromial and bi-cristal diameters.
- b) Incidence of hypothyroidism and sterility.
- c) Incidence of second malignancies.
- d) Complications following staging celiotomy and splenectomy, immediate and remote, including fulminating infections.
- e) Effectiveness of penicillin prophylaxis in the prevention of post-splenectomy infectious complications.

Technical Approach: Initial therapy for all patients will be irradiation, either IF or EF. Therapy must be initiated within 28 days of the staging celiotomy.

Involved regions should be treated to a total basic tumor dose of 3500-4500 rad at a rate of 850-1000 rad tumor dose per week. Additional or "booster" treatment may be given for residual disease through very limited fields at the same or a slightly higher tumor dose rate for a total of 500-1000 rad, provided the tolerance of the normal tissues is not exceeded. Doses over 4000 rad delivered in 4 weeks should be avoided in the spinal cord, gastrointestinal tract and heart.

In patients randomized to receive MOPP therapy, it is recommended that the lower limit of the tumor dose described on previous page be employed, i.e., 35 rad in 20 fractions in 4 weeks.

For extended field radiotherapy the lower limit of radiation dose i.e., 3500 rad in 20 fractions is recommended.

Radiation Dose Modifications for extended field radiotherapy:

<u>Age (Years)</u>	<u>Dose</u>
≥ 11	3500 rad in 20 fractions in 4 weeks
6-10	3000 rad in 20 fractions in 4 weeks
≤ 5	2500 rad in 20 fractions in 4 weeks

Chemotherapy treatment schedule:

Within 4 weeks following the completion of IF radiotherapy, patients randomized to receive adjuvant chemotherapy will begin MOPP chemotherapy (6 courses) provided the adequacy of the hematologic status has been demonstrated by a white blood count $>4,000 \text{ mm}^3$ and a platelet count $>100,000 \text{ mm}^3$.

M Nitrogen Mustard	6 mg/m ² I.V. d 1 & 8.
O Vincristine	1.4 mg/m ² I.V. d 1 & 8.
P Procarbazine	50 mg p.o., d 1; 100 mg/m ² /d p.o., in 2 or 3 divided doses, d 2-14.
P Prednisone	40 mg/m ² /d p.o., in 3 divided doses, d 1-14; FIRST AND FOURTH COURSES ONLY.

Subsequent courses and dosage adjustments: Following the initial MOPP course, subsequent courses will be initiated on days 29, 57, 85, 113 and 141 provided the white blood count is $>4000/\text{mm}^3$ and the platelet count is $>100,000/\text{mm}^3$. If the counts are below these levels, treatment will be delayed and doses adjusted on the subsequent course as shown below:

Day 29 WBC $>4000 \text{ mm}^3$ - Proceed with full dose MOPP, ie 100% all drugs.
Platelet $>100,000 \text{ mm}^3$

29 WBC $<3000 \text{ mm}^3$ - Wait 3 days and repeat blood count.
Platelet $<100,000 \text{ mm}^3$

32 WBC $>4000 \text{ mm}^3$ - Proceed with full dose MOPP, ie 100% all drugs.
Platelet $>100,000 \text{ mm}^3$

32 WBC $<4000 \text{ mm}^3$ - Wait 3 or 4 days and repeat blood count.
Platelet $<150,000 \text{ mm}^3$

35 or 36 WBC $>3000 \text{ mm}^3$ - Full dose VCR & Prednisone
Platelet $>100,000 \text{ mm}^3$ 50% dose HN₂ & Procarbazine.

WBC 2,000-3000 mm^3 - Full dose VCR & Prednisone
25% dose HN₂ & Procarbazine.

WBC 1000-2000 mm^3 - 50% VCR; no HN₂ or Procarbazine.

Day 35 and 36 (cont'd)

Platelet 50,000-100,000 mm^3 - Full dose VCR & Prednisone;
25% HN_2 and 25% Procarbazine.

<50,000 mm^3 - No therapy.

When patients have first relapse they may receive another 6 courses of MOPP chemotherapy.

Progress & Results: No patients have been entered at WRAMC

Conclusions: None

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of : Interim

Work Unit No.: 1555

Title of Project: CALGB Protocol #0702 (Pilot Study), Evaluation of Galactitol 1, 2:5, 6-Dianhydro in the Treatment of Advanced Carcinoma of the Lung and Melanoma. Addendum #1.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine the antitumor effect of galactitol in small cell, large cell, squamous and adenocarcinoma of the lung and melanoma.

Technical Approach: Chemotherapy Regimen:

Patients who have received prior cytotoxic chemotherapy will be required to wait three weeks from the date of the last dose of chemotherapy before starting on Galactitol.

Galactitol Dosage: 60 mg/m² as a slow intravenous push every seven days.

Dose Modifications:

<u>WBC (mm³)</u>	<u>Platelets (mm³)</u>	<u>Dose</u>
>4000	>100,000	Full
3-4000	75-100,000	75%
2-3000	50-75,000	50%
<2000	<50,000	Wait for counts to recover

Dose Adjustment: If after four injections of Galactitol the white blood cell count does not nadir below 4,000 or the platelet count below 100,000, the dose of Galactitol will be increased to 75 mg/m² intravenously each seven days.

Concomitant Therapy: Concurrent use of steroids, antibiotics or other treatment modalities to be used as indicated.

Palliative radiation to be used as indicated. This does not remove patient from study unless it is used to control progressive disease or all the measurable disease.

Progress & Results: WRAMC entered 14 patients, one of whom had melanoma.
None of these have had a significant response.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1556

Title of Project: ALGB Protocol #7721 - Add. #2: A comparative Study of Adriamycin vs Daunorubicin at Two Dose Levels for Induction and of 4-Week Cycle versus 8-Week Cycle for Maintenance Chemotherapy in Acute Myelocytic Leukemia by Cancer and Leukemia Group B.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: A. Inductions Phase:

1. To test whether Daunorubicin at a reduced dose of 30 mg/M^2 produces complete remissions with the same frequency as Daunorubicin at the standard dose of 45 mg/M^2 , and whether the same duration of remission and the same survival are produced by both doses.
2. To test whether another anthracycline, Adriamycin, at a dose of 30 mg/M^2 produces complete remissions with the same frequency as Daunorubicin at the standard dose of 45 mg/M^2 , and whether the same duration of remission and the same survival are produced by both doses.

B. Maintenance Phase:

1. To test whether the duration of remission is equivalent in patients receiving maintenance chemotherapy at 8 week intervals when compared with patients receiving maintenance every 4 weeks. The comparison will also be made with respect to survival from onset of the protocol and from the onset of maintenance.
2. To test whether prolonged exposure to anthracyclines (Daunorubicin and Adriamycin) in maintenance, as achieved by the use of reduced doses (30 mg/M^2), increases the duration of remission as compared to the standard dose of Daunorubicin (45 mg/M^2) given to the same cumulative total dose.

Technical Approach: Induction Phase Treatment Schedules

Regimen I: daunorubicin $45 \text{ mg/M}^2/\text{day}$ by rapid IV injection on days 1, 2, and 3 plus

cytosine arabinoside $100 \text{ mg/M}^2/\text{day}$ by continuous IV infusion on days 1 through 7.

Regimen II: daunorubicin 30 mg/M²/day by rapid IV injection on days 1, 2 and 3 plus

cytosine arabinoside 100 mg/M²/day by continuous IV infusion on days 1-7.

Regimen III: adriamycin 30 mg/M²/day by rapid IV injection on days 1, 2 and 3 plus

cytosine arabinoside 100 mg/M²/day by continuous IV infusions on days 1-7.

Prior to induction patients must have the following procedures completed:

Skin tests - PPD, mumps, dermatophytin, SKSD (see 7.2) and measure reaction.

Lumbar puncture (see 4.7). Enter results of special stains on flow sheets.

A Quantitative immunoelectrophoresis (performed at diagnosis), at first M1 marrow and every four months thereafter.

First induction course should not be shortened for hematologic reasons.

Subsequent induction is as follows:

Bone marrow aspiration seven days after completion of first induction course

Repeat marrow aspiration if first is aplastic or hypocellular and contains 5% or less leukemic cells (one week after first aspiration)

When cellularity returns to normal with 5% or fewer leukemia cells randomize for maintenance therapy

If marrow contains more than 5% leukemic cells and cellularity is 1+ or greater give second course Ara-C 100 mg/m² continuous IV infusion for five days and anthracycline previously used by rapid IV injections on days 1 and 2 only of the second course

Bone marrow aspiration 7 days after completion of second induction

Give third induction course if marrow again contains more than 5% leukemic cells and cellularity is 1+ or greater

If significant marrow hypoplasia occurs, randomize to maintenance

If severe toxicity occurs during first or second induction and recovering marrow is M2 randomize to maintenance

Failure to achieve at least M2 marrow after recovery from third course constitutes treatment failure - patient off protocol

Drug Dose Modification - Induction Phase

Leukopenia: The production of leukopenia is necessary and desirable in remission induction. The initial seven and three-day course should not be reduced based upon peripheral blood count. The decision to give a first course of treatment is a full commitment. The decision to give a second or third course is made seven or more days after the completion of the previous course and is based on the marrow findings, number of leukemic cells in the bone marrow and the cellularity of the bone marrow.

Thrombocytopenia: Depression of the platelet count may be due to progressive disease or to drug toxicity. Drug-induced thrombocytopenia is frequently encountered during treatment with Ara-C and Daunorubicin or Ara-C and Adriamycin and replacement therapy with platelets is

Drug Dose Modification - Induction Phase (Cont'd)

mandatory. If platelets are not available and hemorrhage ascribable to thrombocytopenia ensue, all drugs should be withheld until platelets are obtained. Platelet transfusions should be given prophylactically to all patients with platelet counts of $20,000/M^3$ or below.

Mucosal Ulceration, Gastrointestinal Toxicity: Severe stomatitis, laryngitis, esophagitis, pharyngitis, uncontrolled nausea and vomiting, diarrhea and gastrointestinal bleeding necessitate discontinuing drugs until improvement has occurred. Drugs may then be resumed, using one-half the prescribed dose of Ara-C for the completion of the prescribed time period. The full dose of Daunorubicin or Adriamycin should be given as prescribed.

Nausea and vomiting should be treated symptomatically.

Increase in bilirubin to greater than 2 mg% or transaminase or alkaline phosphatase level to twice the baseline after the initial course of chemotherapy necessitates consideration of possible drug toxicity. If these changes appear to be due to drug toxicity rather than to complications of leukemia, Ara-C and Adriamycin or Daunorubicin doses should be decreased to 50% of the previously used dose.

Renal Dysfunction: High urine flow is desirable as prophylaxis against hyperuricemia, hyperphosphatemia, and hyperkalemia during remission induction in all patients. For actual or anticipated hyperuricemia, allopurinol therapy should be instituted. For uric acid nephropathy, the pH of the urine should be rendered alkaline with intravenous acetazolamide (Diamox). In the presence of urate nephropathy, the injection of bicarbonate and possibly of Mannitol may be of benefit in patients who can tolerate the increased osmotic load. If impairment of renal function develops, antileukemic therapy should be interrupted for clarification of the cause of renal toxicity and to attempt to restore kidney function.

The total cumulative dose of Adriamycin or Daunorubicin should not exceed $550 \text{ mg}/M^2$. Because the total dose expected during induction therapy will not exceed this amount, no cumulative cardiac toxicity is anticipated. Any cardiac abnormalities should be treated by the usual means of rest, Digitalis, diuretics, salt restrictions and anti-arrhythmics, if necessary.

Alopecia: Hair loss occurs very frequently with Adriamycin or Daunorubicin administration so that patients should be forewarned about this probability. A scalp tourniquet that provides lower drug levels for the hair roots also provides a sanctuary for leukemic cells and should not be used.

Patients will be placed on maintenance regimens after completion of induction phase.

Maintenance Regimens:		ANTHRACYCLINE & DOSE (INDUCTION & MAINTENANCE)	DISCONTINUE ANTHRACYCLINE AFTER MAINTENANCE COURSE #		
REGIMEN	<u>TIME INTERVAL BETWEEN MAINTEN- ANCE COURSES (WEEKS)</u>				
AI	4	DNR 45 mg/M ²	15	11	7
AII	4	DNR 30 mg/M ²	27	23	19
AIII	4	ADR 30 mg/M ²	27	23	19
BI	8	DNR 45 mg/M ²	15	11	7
BII	8	DNR 30 mg/M ²	27	23	19
BIII	8	ADR 30 mg/M ²	27	23	19

If 1 course was required for Induction

If 2 courses were required for Induction

If 3 courses were required for Induction

Dose modification - Maintenance Phase:

Marrow status: The bone marrow must be aspirated monthly just prior to each new course to determine whether the patient is still in remission. More frequent bone marrow examinations may be indicated by abnormalities in the blood count or clinical status.

Leukopenia and Thrombocytopenia: If granulocytes are greater than 2000/cm and there is no active infection and platelets are greater than 100,000/cm, give 100% of scheduled dose in the second maintenance course at the scheduled time.

If neutrophils or platelets are below these threshold values or if infection is present, delay one week and repeat blood counts.

If counts have recovered above threshold values at one week and/or infection is controlled, proceed at full dose.

If counts are still below threshold values, at one week and maintenance course is due to start but marrow cellularity is 2 or greater, give 50% dose of all drugs for next course.

If counts are still below threshold values at one week after maintenance course is due to start and marrow cellularity is less than 2, continue to withhold drugs until marrow cellularity reaches 2 or counts satisfy threshold values, then give 50% dose of all drugs.

Severe marrow hypoplasia (leukopenia 100/ul or marrow cellularity of 0-1+) associated with severe infection justifies 50% dose reduction in Ara-C, TG, DNR or Adr, despite hematologic recovery.

Neurologic Toxicity: The dose of vincristine should be decreased to 50% for disappearance of deep tendon reflexes only if this is accompanied by diminution of muscle strength or persistent paresthesias. For more severe disability, (specify in the remarks), the vincristine should be omitted until recovery begins, at which point 50% of dose should be reinstituted.

Corticosteroid Toxicity: Prednisone will be temporarily withheld or tapered rapidly, or decreased to one-half dose (specify in remarks) for:

- a) active peptic ulceration;
- b) severe diabetes mellitus poorly controlled by insulin
- c) steroid psychosis or hypomania

Hepatic Toxicity or involvement: If bilirubin is greater than 3 mg% but less than 5 mg% give 50% of vincristine, TG, adriamycin and daunorubicin. If bilirubin is greater than 5 mg% omit vincristine, TG, daunorubicin and adriamycin.

Cardiac Toxicity: The maximum dose of DNR and ADR that a patient can receive in any arm of this protocol is 510 mg/M². At this dose, cardiac toxicity is not anticipated. Any cardiac abnormality should be treated by the usual means of rest, digitalis, diuretics and anti-arrhythmics if necessary, and DNR (or ADR) should be discontinued.

Progress & Results: WRMC entered 11 patients. One is too early for evaluation. Five had no response and died from 3 to 31 days after entry on the protocol. Four went into a complete remission, and are in complete remissions from 84 to 303 days. One had a partial remission, subsequently relapsed and died on day 337.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1557

Title of Project: CALGB Protocol # 0704 (Pilot Study): A Phase II Trial of Neocarzinostatin in Carcinoma of the Bladder, Kidney, Pancreas, Stomach, Uterus, Ovary, Hepatoma, Acute Leukemia, or Malignant Melanoma.

Investigators:

Principal: Johannes Blom, M.D.

Associate: M. Robert Cooper, M.D.
Robert L. Comis, M.D.

Objectives: To evaluate response rate, duration of response and survival of patients with acute leukemia, pancreatic, stomach, bladder, ovarian, uterine, liver and renal carcinoma, and malignant melanoma treated with a new agent, neocarzinostatin (NCS). To determine the frequency and severity of different organ system toxicities in patients with advanced cancer treatment with neocarzinostatin.

Technical Approach:

Patients with acute leukemia (all types) receive the following treatment:

Neocarzinostatin 2500 U (2.5 mg.)/M²/day I.V. bolus over 30 minutes x 5 days, repeated at intervals of 7-10 days if necessary to obtain a remission (3 courses of 5 days considered an adequate trial.)

All patients with solid tumors of pancreas, liver, stomach, kidney, bladder, ovary and uterus, and malignant melanoma meeting the eligibility requirements who have received prior chemotherapy or radiotherapy will start at 1500 U (1.5 mg.)/M²/day x 5 days and, if tolerated, the dose will be increased in the next course to 2250 U (2.25 mg.)/M²/day x 5 days. Patients not previously treated with chemotherapy or radiotherapy will start at 2250 U (2.25 mg.)/M²/day x 5 days.

Courses will be repeated every 35 days.

Neocarzinostatin will be discontinued if no response is seen after three courses.

Drug Modifications:

Hematologic Toxicity: Modifications according to changes in WBC and platelets will be made as outlined on next page for solid tumors.

<u>If WBC is</u>	<u>and/or platelets</u>	<u>Dose</u>
$\geq 4,000$	$\geq 120,000$	100%
3,000 - 4,000	80,000 - 120,000	50%
$\leq 3,000$	$\leq 80,000$	Hold Rx

Renal Toxicity: Omit therapy if serum creatinine rises to ≥ 2.0 mg%. Resume at 50% dosage if toxicity clears (i.e. serum creatinine ≤ 1.6 mg%). If toxicity persists discontinue therapy.

Gastrointestinal Toxicity: If nausea and/or vomiting are severe, omit therapy until symptoms clear and resume at 50% dose.

Skin and Systemic Toxicity: If a severe skin rash develops or a high fever develops uncontrolled with antipyretics, or antihistamines, discontinue therapy. Significant hypotension and/or anaphylaxis or anaphylactoid reactions are a reason to discontinue therapy.

During treatment of neocarzinostatin the following procedures should be obtained:

For Acute Leukemia: Repeat bone marrow at 2 - 4 weeks after initiation of induction therapy. Daily CBC and platelet count. SMAC-20 x 3/wk or sooner.

For Solid Tumors: Repeat chest x-ray or scan or sonogram required to evaluate indicator lesions prior to each cycle of chemotherapy. Daily CBC and platelets during therapy and SMAC-20 weekly or sooner if indicated. For pancreas and stomach cancer, follow-up CEA values are indicated. A CBC and platelet count should be obtained every 2 weeks following therapy.

Progress & Results: Six patients have been entered at WRAMC. One of whom is too early for evaluation. One patient had stable disease and the other four progressive disease. All patients have expired.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1558

Title of Project: CALGB Protocol #7761, A Study to Determine the Effectiveness of Single versus Multiple Alkylating Agents with or without Adriamycin in the Primary Treatment of Multiple Myeloma.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To test the hypothesis that three alkylating agents given sequentially produce

- i) higher frequency of good response
 - and ii) longer duration of disease control
- than the same alkylating agents given in combination.

To test the hypothesis that addition of adriamycin to a combination of three alkylating agents

- i) increases the frequency of good response
- and ii) prolongs the duration of disease control

To test the hypothesis that

- i) the frequency of good response
 - and ii) the duration of disease control
- are the same after treatment with intravenous L-PAM as after treatment with triple alkylating agents.

To compare the duration of remission maintained with Oral L-PAM in patients induced with combination chemotherapy regimens and with I.V. L-PAM, and to compare duration of disease control with these regimens against historical controls maintained on intravenous therapy with triple alkylating agents.

To evaluate psychosocial function in patients with myeloma before and during treatment and to investigate differences in psychosocial function in patients receiving different treatment.

To determine if new experimental regimens prolong the survival of patients with multiple myeloma compared to historical controls.

Technical Approach:

Regimen I Combination Alkylating Agents plus prednisone

L-PAM 8 mg/m² I.V. on day 1
Cyclophosphamide 300 mg/m² I.V. day 1
BCNU 100 mg/m² I.V. day 1



BUN >30/
creatinine >1.5
give 1/2 dose

Each cycle = 6 weeks
Repeat for 12 cycles (72 weeks)

Prednisone during first 6 weeks only

0.8 mg/kg p.o. single dose days 1-14
0.4 mg/kg p.o. single dose days 15-28
0.2 mg/kg p.o. single dose days 29-42

D/C after day 42

Begin maintenance therapy in 73rd week

Regimen II Sequential Alkylating Agents plus prednisone

L-PAM 16 mg/m² I.V. day 1
Cyclophosphamide 600 mg/m² I.V. day 22
BCNU 150 mg/m² I.V. day 43

BUN > 30/
creatinine > 1.5
Give 1/2 dose

Each cycle - 12 weeks
Repeat for 6 cycles (72 weeks)

Prednisone during first 6 weeks only (see Regimen I)

Begin maintenance therapy in 73rd week

Regimen III Combination Alkylating Agents plus adriamycin plus prednisone

10 courses { L-PAM 8 mg/m² I.V.
Cyclophosphamide 300 mg/m² I.V.
BCNU 100 mg/m² I.V. }

Days 1, 43, 106, 148, 211, 253, 316,
358, 421, 463

4 courses } Adriamycin 45 mg/m² I.V. days 85, 190, 295, 400

Prednisone (as per Regimen I)

Begin maintenance therapy in 73rd week

Regimen IV I.V. L-PAM plus prednisone

L-PAM 16 mg/m² I.V. days 1, 15, 29, 43, 71 and every 4 weeks
thereafter until day 491/then D/C

Total of 20 doses

Prednisone as per Regimen I

Begin maintenance therapy in 73rd week

MAINTENANCE THERAPY

L-PAM 0.05 mg/kg p.o. daily until relapse, progression of
disease, or 2 years from day 1 of induction

Progress & Results: WRAMC entered 3 patients, one is too early, one expired on day 40 and one has stable disease on day 49.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1559

Title of Project: CALGB Protocol 7781 - Add. #3: Small cell carcinoma of the lung: Localized disease. A phase III study. Combination chemotherapy vs alternating chemotherapy plus radiotherapy with or without immunotherapy.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To test whether chemotherapy (with either of two combinations of agents) and radiotherapy (to the primary site and brain) produce a higher frequency of response (complete and partial) in patients with localized small cell (oat cell) carcinoma of the lung, as compared to historical controls.

To test whether combination chemotherapy and radiotherapy produce longer durations of response in these patients, as compared to historical controls.

To test whether combination chemotherapy and radiotherapy affect patterns of relapse in these patients, as compared with historical controls.

To test whether combination chemotherapy and radiotherapy prolong survival in these patients, as compared to historical controls.

To test whether the two combinations of drugs, used with radiotherapy, have significantly different effects on:

- i) frequency and/or duration of response
- ii) pattern of relapse or
- iii) survival in patients with localized small cell carcinoma of the lung

To test whether immunotherapy with MER (Methanol extraction residue of Bacillus Calmette-Guerin), added to combination chemotherapy (with either of two regimens) significantly affects:

- i) duration of response and/or
- ii) pattern of relapse and/or
- iii) survival

In patients with localized small cell carcinoma of the lung initially responsive to combination chemotherapy and radiotherapy.

To evaluate psychosocial function in patients with localized small cell carcinoma of the lung before, during, and after treatment, using:

- i) the rating of psychosocial function;
- ii) the handicap rating scale;
- iii) the profile of mood states;
- iv) Demographic data.

Technical Approach: Prior to patient being randomized for induction, at the completion of induction and on Day 304 the following skin tests must be performed: PPD, Dermatophytin "O" and "Streptokinase-Streptodornase: Waridase".

INDUCTION PHASE:

Regimen I: Patients will receive the following drugs:

Methotrexate	30 mg/M ² IV
Adriamycin	35 mg/M ² IV
CCNU	30 mg/m ² po
Cyclophosphamide	400 mg/M ² IV

All drugs are given on the first day of the cycle.

Two cycles of chemotherapy will be given, on Days 1 and 21, followed by radiotherapy in a split course technique (The first part of a split course of radiotherapy will consist of 2500 rads in 10 treatment days beginning on Day 42. This will be followed by a two week rest period. Then, 2000 rads will be given in a further 10-day period beginning on Day 70. In addition, 3000 rads in 10 treatments will be given to the whole brain of all patients entered into this study.), to be followed by two further cycles of chemotherapy on Days 84 and 105.

Adriamycin is omitted from the third cycle of MACC, which is given one week after the completion of radiotherapy. This should prevent the exacerbation of radiation esophagitis and esophageal stricture formation. Adriamycin will be reinstituted on day 105 at the beginning of the fourth cycle of chemotherapy.

Regimen II: Patients will receive the following drugs:

The first course given on Day One is:

Cyclophosphamide	700 mg/M ² IV
CCNU	70 mg/M ² <u>po</u>
Vincristine	1.0 mg/M ² IV (No greater than 2.0 mg in any single dose will be given)

On Day 21 of each six week cycle:

Adriamycin	50 mg/M ² IV
Vincristine	1.0 mg/M ² (No greater than 2.0 mg in any single dose will be given)

As in Regimen I, radiotherapy will begin on Day 42 by the split course technique (See description of split course technique in Regimen I), chemotherapy will be reinstituted on Day 84.

The induction phase of this protocol consists of four cycles of chemotherapy, two prior to the institution of radiotherapy, and two subsequent to the completion of radiotherapy.

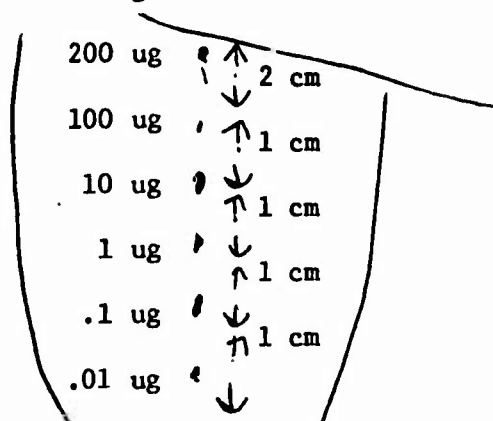
MAINTENANCE PHASE

At day 136, patients will be restaged and an assessment of their performance status and response will be made. All patients who have evidence of progressive disease prior to this point will go off protocol. All patients who have had an objective response or no change will be randomized to receive addition chemotherapy or chemo-immunotherapy.

Regimen A: Patient should continue with his initial chemotherapy (Reg I. or Reg II) at three week intervals.

Regimen B: Patient should continue with his initial chemotherapy (Reg I. or Reg II) and in addition, receive immunotherapy with MER given every six weeks, starting on the day of the randomization and coinciding with first maintenance course of chemotherapy.

MER dosages:



At the time of the first scheduled administration, 200 ug of MER should be injected intradermally into each of three (3) sites on the anterior body surface. Sites should be chosen so that each site is drained by a different group of lymph nodes. In addition, doses of 200, 100, 10, 1, 0.1, and 0.01 ug should be injected in a linear array of sites on an anterior thigh as illustrated above:

Acceptable sites for MER injection, in addition to the proximal thighs, are the upper and lower abdominal wall and the infraclavicular areas. Sites where the regional lymphnodes have been excised or irradiated should not be used. Areas which might be irritated by friction from clothing, etc should be avoided.

Radiation Therapy: Evaluation of the area to be irradiation must be made prior to commencing chemotherapy. The volume to be included in the irradiated field is defined as the original tumor size and its drainage because recurrence may develop in any part of the area of original involvement despite marked shrinkage after two courses of chemotherapy.

Radiation therapy to the primary tumor will commence on Day 42 after two courses of chemotherapy. Radiotherapy will be given by a split course technique using two weeks for the first course a two week rest, and then two weeks for the final course.

Radiation of megavoltage quality (1 MeV or greater) will be used preferably with an isocentric gantry apparatus with a source to axis distance greater than or equal to 80 cm.

Radiotherapy portals shall include the primary disease site, the whole width of the mediastinum extending superiorly above the supersternal notch and inferiorly 4 cm. below the carina. More generous margins may be desirable superiorly for upper lobe lesions and inferiorly for lower lobe lesions. With this field coverage, subcarinal lymphnode groups as well as groups of lymph nodes of the lymphatic drainage of the thoracic duct will be covered. The supraclavicular fossi bilaterally, will be include in all cases using an anterior field only.

The tumor dose will be 2500 rad in 10 sessions over two weeks. AP PA parallel opposing fields will be used. Following a two week rest period, an additional 200 rad in 10 sessions to the same volume will be delivered. This is designed to give a TDF of 75.

Dose calculations shall be done on the basis of midplane doses, i.e., the dose to the central axis point midway between the anterior and posterior entrance points. The dose to the spinal cord at the suprasternal notch should be calculated and recorded in each patient. For sharply sloping chests, it may be necessary to calculate the dose in more than one plane. If a variation in the midplane dose of more than 10% at the different planes is noted, a compensator will be required. If tissue compensation is employed, it should be clearly indicated in all the records sent to the Radiotherapy Office.

The supraclavicular fossi will receive a given dose of 4500 rads + 5%, calculated at a depth of 3 cm. The dose of these areas should be calculated and recorded as reference doses into the Radiotherapy Reporting Forms. The depth of the recorded dose should be 3.0 cm from the skin surface. This will require the addition of boosts to the supraclavicular fossae only. The inferior border is defined as the lower edge of the clavicle at the sternoclavicular joint.

During the second course of treatment the field arrangement should be appropriately modified so that no part of the spinal cord receives a dose in excess of 4200 rads (or a TDF of 69).

If field arrangements other than AP PA parallel opposed portals are to be used, the dose distributions are to be calculated and isodose maps are to be plotted at the midplane and at other planes of interest.

For purpose of this study, no corrections are to be applied for lung or bone attenuation. Doses will be described in rads to muscle.

Modification of Radiation Dose: Patient's general disability or deterioration may call for interruption or cessation of treatment. The reason should be stated and any modification of time/dose relationship should be accounted for by adjusting the daily dose rate and/or total dose in order to achieve a TDF of 75. Radiotherapy should not be started or should be stopped if the white blood count falls below 1000 or the platelets fall below 30,000. Hemoglobin levels below 10 gm. should be corrected by transfusion without interruption of radiation therapy. Radiation therapy may be temporarily stopped if severe esophagitis occurs.

Prophylactic Whole Brain Radiation: Radiation of megavoltage quality (1 MeV or greater) will be used.

With the patient in a supine position, the parallel opposed lateral portals will be used. The field will include the entire cranial content. The inferior margin of the field will pass through the supraorbital ridge, the external auditory canal and C2 vertebra. Parallel opposed fields will be employed. Each field will be treated every day.

The tumor dose will be 3000 rads administered in 10 treatments over 12 days. The dose will be calculated midway between the lateral entrance points on the central axis. This will deliver a TDF of 62. Rarely, transient dementia has been observed in patients who have received prior chemotherapy when this dose and schedule of brain irradiation has been given. Equally rare has been the observation of transient dementia when chemotherapy has followed the irradiation.

Dose Modifications: CCNU, cyclophosphamide, adriamycin and methotrexate, and concurrent therapy:

Hematologic Toxicity: On day of scheduled course:

<u>If Leukocyte Count</u>		<u>Platelets are</u>	<u>Then Give</u>
> 4000	and	> 150,000	100%
3500-4000	or	< 100,000	75%
2500-3500	or	> 75,000	50%
2500-3000	or	> 75,000	25%
< 2500	or	< 75,000	Delay dose until WBC has reached appropriate levels.

Hepatic Dysfunction: If on Day of Therapy:

<u>The bilirubin or SGOT</u>		<u>Give Indicated Percentage Dose of</u>					
(mg%)	(iu)	ADM	CYT	MTX	CCNU	MER	VIN
Is < 2.0	is < 60	100	100	100	100	100	100
2.1-4.0	60-150	50	75	75	75	100	50
> 5.0	> 150	0	0	0	0	0	0

Renal Dysfunction

<u>If Creatinine</u> (mg%)	<u>Give Indicated Percentage Dose Of</u> MTX
Is within normal limits (≤ 1.5)	100
1.5-2.0	50
> 2.0	25

Neurologic Toxicity

If deep tendon reflexes are absent and/or there is mild paresthesia with no loss of muscle strength, give 75% of vincristine dose.

If deep tendon reflexes are absent and/or there is plus moderate or severe paresthesia and/or diminution of muscle strength down to 50% of expected, give 50% of vincristine dose.

For severe disability or for ileus or urinary retention, omit vincristine until recovery is noted. After recovery, restart at 50% dose.

Bladder Toxicity:

Cyclophosphamide can cause severe hemorrhagic cystitis and fibrosis of the bladder. These effects can be minimized by good hydration using a diuresis of approximately 2-3 liters over 18 hrs following the administration of the drug, plus frequent bladder emptying. Should this side effect occur, subsequent courses may be given at half (50%) dose or with the use of acetylcysteine (Mucomyst^R) instillation into the bladder.

Gastrointestinal Toxicity

If oral-pharyngeal ulcers are present on the day of treatment, methotrexate and adriamycin should be temporarily omitted, and cyclophosphamide given at half (50%) dose until the oral-pharyngeal ulcers are cleared. Subsequent doses of adriamycin and methotrexate will restart at 50% dose.

Cardiotoxicity

Appearance of congestive heart failure or a persistent arrhythmia is an indication to discontinue adriamycin. Such toxicity is unusual at a cumulative dose level below 550 mg/M², however, there may be additive effects or synergism with radiation therapy and cyclophosphamide. Electrocardiographic changes, lowered QRS complex, non-specific ST wave changes may appear, and further adriamycin should be used with caution subsequent to this. Perhaps a better mechanism for determining the onset of adriamycin toxicity is the measurement of systolic time intervals, or the ejection fraction as determined by echocardiography.

Alopecia

Alopecia is universal with the drugs and brain irradiation being used.

MER dose modifications and toxicities:

The titration site on the anterior thigh should be observed 1 to 3 weeks after the initial administration of MER. The smallest dose of MER which produced areas of induration 1 cm in diameter, with minimal or no central necrosis, should be used for subsequent courses of treatment with MER. That dose should be injected intradermally into each of five (5) sites drained by different groups of lymph nodes. All subsequent doses of MER should also be injected in these sites; however, new injections should be at least 1 cm distant from previous injections in the same area.

If patient develops increasing sensitivity to MER, as evidenced by increasing induration and/or ulceration at the injection sites, the titration should be repeated using 100%, 10%, 1%, 0.1%, 0.01%, and 0.001% of the dose established by the previous titration.

MER will be administered during the maintenance phase at six week intervals from days 136-304, and at eight week intervals from day 360 to day 696. Initial dose will be 1.0 mg as described (MER dosages). Further dose modification will be as described above.

MER Toxicity

Allergic Reactions: Systemic allergic reactions are extremely rare but would be an indication to omit MER permanently. Such reactions should be treated with epinephrine and/or steroids if anaphylactic, in addition to any other clinically indicated therapy. Severe reactions should be reported immediately to the study chairman.

Local Pain: Pain at the injection site is to be anticipated and should be treated with appropriate analgesics; it is not an indication to withdraw therapy. However, if ulcers greater than 1 cm in diameter occur, further dose titration should be performed.

Fever: Post vaccination febrile episodes and chilliness may occur and should be allowed to run their course or be treated with antipyretics. They are not an indication to stop therapy.

RADIATION Toxicity

Hematologic toxicity: will not be experienced at these dose levels. A low white count and platelet count at beginning of treatment should not alter the planned treatment doses, but will be assumed to be chemotherapeutically induced.

Skin Reaction: some erythema will be experienced at these doses but this will not lead to severe changes requiring any particular treatment.

Adriamycin enhancement and recall: in those patients who have had adriamycin prior to radiotherapy, then enhancement of the skin erythema and severe esophagitis may be experienced. In those patients who are given adriamycin after radiotherapy, both the skin erythema and esophagitis may return, and the patient should be both informed of the possibility and aware of the cause. Treatment is symptomatic only and the problems are only temporary.

Cardiotoxicity: not normally observed at these dose levels, will have to be watched for with the addition of adriamycin.

CONCURRENT THERAPY:

Transfusion of blood and platelets and treatment with antibiotics, allopurinol, acetazolamide, phenothiazines, heparin and other drugs are permitted where indicated. The reasons for the use of ancillary therapy, the doses employed and duration of therapy shall be indicated on the flow sheet.

EVALUATION OF PSYCHOSOCIAL FUNCTION:

Rating of psychosocial function (RPF): This is done by the physician.

Handicap rating scale: This is done by the physician.

Profile of Mood States (POMS): On PSY-2 Form.

Demographic data: Supplied by patient.

Ratings will be obtained:

- 1) Prior to treatment
- 2) At the conclusion of radiotherapy
- 3) At the time of randomization for MER
- 4) and at the time of relapse; when 50% of patients have relapsed, the remaining patients will be rated.

Progress & Results: WRAMC entered six patients. Four patients have stable disease from 92 to 212 days. One patient expired and one is off study on day 60.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1601

Title of Project: WPAAC Protocol 7207 - Add. 0: Use of pentamidine isethionate in pneumonia caused by or suspected to be caused by pneumocystis carinii.

Investigators:

Principal: Johannes Blum, M.D.

Objectives: Treatment of pneumonia caused by or suspected to be caused by pneumocystis carinii with pentamidine isethionate.

Technical Approach: Pentamidine isethionate 4 mg/kg I.V. for 12-14 days.

Progress and Results: Six patients have been entered, five of whom had good clearing of the infiltrative process. The sixth patient had pulmonary hemorrhage at autopsy and no evidence of pneumocystis.

Conclusions: As has been demonstrated by many investigators, pentamidine is an effective drug in the treatment of pneumocystis carinii pneumonia. No new patients have been placed on study since Nov 1974, as other drugs have become available. However, pentamidine isethionate remains a very useful agent.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1602

Title of Project: WRMC Protocol 7301 - Add. 0: The Use of
Cholestyramine in Metastatic Carcinoma of the
Prostate and Ovary and Other Malignancies.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To observe response in metastatic carcinoma of the prostate
and ovary and other malignancies.

Technical Approach: Cholestyramine (questran) 4 mg (one packet) placed
in a preferred beverage three times daily. Because
of interference with the absorption of lipid soluble
vitamins, 2 ml of polyvisol will be administered
daily.

Progress & Results: Four patients have been entered on study. Three
had no response or progressive disease. One has
had minimally progressive disease for about 18
months. One patient was recently entered who had
subjective improvement.

Conclusions: No new patients have been entered on study. This study
was closed.

Funding Requirements, FY-78: See introductory remarks to Annual
Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1605

Title of Project: WRMC Protocol 7206 - The Use of Methyl-CCNU (1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea-1)(NSC 95441) in the Treatment of Brain Tumors.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Patrick R. Bergevin, MAJ, MC

Objectives: To evaluate the effectiveness of MeCCNU in the treatment of CNS tumors as measured by tumor shrinkage with possible neurological improvement and duration of survival.

Technical Approach: Patients are divided into good risk and poor risk groups. The good risk group will receive adriamycin 60 mg/m² and DIC 250 mg/m² for 5 days. The poor risk group will receive adriamycin 45.0 mg/m² and DIC 200 mg/m² for 5 days.

Progress & Results: Fifty-five patients have been entered on study. Six are lost to follow-up or no recent information is available; 9 patients had either metastatic disease or no histologic information of primary brain tumor. 29 patients were begun on treatment after completion of surgery and radiation to the brain. Two of these had Grade II astrocytomas with recurrence for which they received further radiation therapy and were then placed on chemotherapy. One relapsed on day 762 and the other on day 889. Four of these 29 patients had Grade II astrocytomas and are stable from 274 to 1355 days, one relapsed on day 577. Twenty patients remained stable or became asymptomatic until they had progressive disease and subsequently expired from 15 to 549 days. The remaining two patients have been stable for 205 and 255 days. Eleven patients were placed on study when they had evidence of progressive disease, one obtained a complete remission and relapsed on day 594. Ten patients remained on study until further progression or death from 37 to 625 days. 24 patients had progressive

disease and almost all expired shortly afterwards. One patient had an improvement of his clinical condition but progression of his disease by day 594. Twenty-two patients were entered on study after surgery and radiation therapy when their condition was stable. Twelve patients relapsed from 19 to 770 days after entry on the study. Five patients remain on study from 180 to 1335 days.

Conclusions: The efficacy of this treatment for patients with active disease is very minimal. The efficacy of the chemotherapy after surgery and radiation therapy will need further evaluation.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1604

Title of Project: WRMC Protocol 7205 - Phase II Protocol Combination Chemotherapy with Dimethyl-Triazeno Imidazole Carboxamide (DIC) and Adriamycin in Soft Tissue and Bone Sarcomas.

Investigators:

Principal: Johannes Blom, M.D.

Associate: A. Richard Miskoff, MAJ, MC

Objectives: 1. To determine the efficacy of combination chemotherapy with DIC and adriamycin in patients with soft tissue and bone sarcomas.
2. To evaluate the toxicity of this combination of agents.

Technical Approach: Treatment regimen for good risk patients:
Adriamycin 60 mg/m² on day 1 in rapid I.V. infusion
DIC 250 mg/m² I.V. daily for 5 days

Treatment regimen for poor risk patients:
Adriamycin 45 mg/m² on day 1 in rapid I.V. infusion
DIC 200 mg/m² I.V. daily for 5 days

Progress & Results: Thirty-eight patients have been entered on the study, 3 patients are lost to follow-up or no recent follow-up is available, 2 patients are not evaluable, 1 patient refused treatment and one was invalid because at autopsy the diagnosis was renal cell. 1 patient had a complete remission, and relapsed at day 677. Four remain in complete remission from 610 to 1147 days. One patient received the treatment as adjuvant, but had progressive disease by day 44, 2 remain in remission at 610 and 431 days respectively. 3 had a partial remission, 10 had progressive disease, 10 had stable disease or no response.

Conclusions: Although patients with a variety of sarcomas have been entered on this study, the overall response rate is rather low. However, many of these patients had far-advanced disease. The study was closed to entry of new patients on 18 May 1978.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1610

Title of Project: WRMC Protocol 7307, Add. 1 - Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast. (NCI B-134)

Investigator:

Principal: Johannes Blom, M.D.

Objectives: Evaluation of dibromodulcitol in patients who have been treated with and are resistant to standard modes of therapy.

Technical Approach: Patients will be treated with dibromodulcitol by mouth on days 1-10 of each 21 day cycle.

Progress & Results: Fifteen patients have been entered on the study. One patient is free of disease on day 757. The study was discontinued in December 1977, because of low blood counts. All other patients had progressive disease.

Conclusions: Twenty-nine patients were entered by all participating institutions. In four patients a response was observed.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: Tormey, D.C., Falkson, G., Perlin, E., Bool, J., Blom, J., and Lippman, M. Evaluation of an intermittent schedule of dibromodulcitol in breast cancer. Cancer Treatment Reports 60 (11): 1593-1596, November 1976.

Type of Report: Interim

Work Unit No.: 1613

Title of Project: WRAMC Protocol 7402 - Protocol for Adjuvant Therapy of Stage II Testicular Carcinoma with Chemotherapy (Actinomycin-D and Chlorambucil), Radiation Therapy or Chemotherapy plus Radiation Therapy after Retroperitoneal Lymph Node Dissection.

Investigators:

Principal: Anthony Borski, COL, MC
Stanley Chism, MAJ, MC
Johannes Blom, M.D.

Objectives: To determine which is the best form of therapy in patients with stage II carcinoma of the testicle after radical lymphadenectomy.

Technical Approach: Patients who had all tumor removed at the time of radical retroperitoneal lymph node dissection are randomly assigned to one of three forms of therapy, radiation therapy, chemotherapy or chemotherapy plus radiation therapy. The chemotherapy will be continued intermittently for three years and will consist of actinomycin-D and chlorambucil. Patients who have residual tumor in the abdomen after radical retroperitoneal dissection are randomized between two forms of therapy, radiation therapy and chemotherapy plus radiation therapy.

Progress & Results: This study was activated in January 1974. Four patients have been entered at WRAMC. Two patients had chemotherapy and two patients had radiation therapy. Both patients who received chemotherapy relapsed. No follow-up is presently available on the patients who had radiation therapy. This was a national study under the auspices of the National Cancer Institute in which several institutions participated, however because of lack of entry of patients onto the study it was discontinued on 26 January 1976.

Conclusions: None

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1621

Title of Project: WRAMC Protocol 7208 - Phase II Protocol 5-Azacytidine
in Acute Leukemia

Investigators:

Principal: Johannes Blom, M.D.

Associate: A. Richard Miskoff, MAJ, MC

Objectives: To determine the effectiveness of 5-azacytidine in the
treatment of acute leukemia.

Technical Approach: 5-azacytidine 250 mg/m² I.V. daily x5 in 3 divided
infusions every 8 hours
This course to be repeated every 2 weeks.

Progress & Results: Fourteen patients have been entered on the study,
1 patient is lost to follow-up, 1 had an in-
adequate treatment, 1 had a complete remission, 1
a partial remission and 10 had no response.

Conclusions: 5-azacydidine is a moderately active agent in patients
with advanced acute leukemia. Experiences in other
institutions indicate a somewhat better response rate
in combination with other agents.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1626

Title of Project: WPMO Protocol 7405, Add. 1 - Treatment of Advanced Renal Cell Carcinoma with a Combination of 1-(chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)(NSC 79037) and Bleomycin (NSC 125066).

Investigators:

Principal: Johannes Blom, M.D.

Associate: Ivan P. Law, MAJ, MC
Daniel H. Cox, MAJ, MC
Bernhard T. Mittenmyer, COL, MC

Objectives: 1. To evaluate the effectiveness of CCNU and bleomycin in the treatment of advanced renal cell carcinoma.
2. To measure survival in patients so treated.

Technical Approach:

Induction: All patients will receive
CCNU 130 mg/m² p.o. every 6 weeks
Bleomycin 15 mg I.V. once a week

Maintenance: All patients who are in complete remission or a partial remission after three courses of induction regimen will receive:
CCNU 130 mg/m² p.o. every 6 weeks
Bleomycin 15 mg I.V. every three weeks, not to exceed the maximum total dose of 210 mg/m²

Progress & Results: Thirty-one patients have been entered on the study, on 4 of these patients no recent follow-up is available, one had inadequate treatment. Ten patients were entered for adjuvant treatment, 2 of whom relapsed at 152 and 222 days. The remaining 8 patients remain without evidence of disease from 483 to 1447 days. None of 16 patients with metastatic disease had a response to the treatment, had progressive disease and subsequently expired. Two patients developed severe pulmonary toxicity with dyspnea after total doses of bleomycin of 180 mg and 270 mg, subsequently both died.

Conclusions: The number of patients entered in the adjuvant group is too few to make any conclusions at this time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Block Unit No.: 1627

Title of Project: WRMC Protocol #7404 - Add. #1: Immunological evaluation and immunotherapy of patients with carcinoma of the lung.

Investigator:

Principal: Johannes Blom, M. D.

Associate: William J. Hein, MAJ, MC, USA
Robert K. Oldham, M. D.
Robert B. Herberman, M. D.

- Objectives:
1. To investigate the therapeutic efficacy of BCG given by dermal scarification in patients with carcinoma of the lung.
 2. To investigate the therapeutic efficacy of the combination of BCG and allogeneic tumor cells in patients with carcinoma of the lung.
 3. To correlate in vitro and in vivo measurements of cellular immunity with the clinical status of the patient.

Technical Approach: Patients are put into three broad groups based on the extent of disease:

A patients - surgically resectable disease (no clinically detectable tumor after surgery)

B patients - 1) surgically treatable for the bulk of tumor but not completely locally resectable (palliative resection) or 2) residual disease treatable by local radiotherapy (after 1) or primary disease treatable by radiotherapy (patients in whom surgery is contraindicated)

C patients - patients with metastatic disease.

Radiotherapy: A) "Curative Intent" - B patients: When no distant metastases are clinically detectable, 5000 rads delivered at 900-1000 rads weekly in divided doses to the primary tumor, adjacent mediastinum and hilar region followed by an additional 1000-1500 rads to the primary tumor only.

3) "Palliative Intent": To be given to the primary site of tumor in all C patients and may be given at the discretion of the physician to local tumor masses in C patients during chemotherapy for metastatic disease if clinical symptoms warrant it. 3000 rads over two weeks will be administered to the local symptomatic area only.

Chemotherapy: A patients - no chemotherapy.

B patients - Will be treated with chemotherapy as C patients after they have finished their radiotherapy.

C patients - All patients will be treated with chemotherapy as follows:

Cytosin 500 mg/M²,
Methotrexate 40 mg/M²,
Vincristine 2.0 mg

total dose intravenously on days 1 and 8 of a 28-day cycle. Chemotherapy will continue for a two-year period. Patients randomized to receive BCG or a BCG plus allogeneic tumor will receive these materials on days 1 and 21 of the 28-day cycle.

Immunotherapy: All patients (group A, B and C) shall be randomized into three groups:

- 1) Control group - no immunotherapy.
- 2) Non-specific active immunotherapy (BCG only) every two weeks by Heaf gun dermal scarification.
- 3) Specific active immunotherapy (BCG + Allogeneic Cells). These patients will receive BCG as outlined above and in addition will receive allogeneic tumor cells in the same extremity at the same visit. These cells will be intradermally and subcutaneously injected adjacent to the BCG scarification.

Progress & Results: Thirty-nine patients have been entered on the study. Six patients were not evaluable because of early death, all with advanced disease. One patient is lost to follow-up. One A patient on BCG relapsed at 715 days and one at 32 days. Nine patients are still on study from 345 to 1425 days. Six A patient controls relapsed from 273 to 760 days. One patient is still on study at 195 days. Four B patients on BCG and chemotherapy relapsed from 48 to 190 days, one patient is still on study at 1206 days. Four B patients on chemotherapy alone relapsed from 27 to 245 days. One patient died at 90 days and one at 281 days without evidence of disease. Two C patients on BCG and chemotherapy had progressive disease and expired at 124 and 186 days. One patient on chemotherapy with the syndrome of inappropriate ADH secretion went into complete remission and expired 7 months later from a pulmonary embolus without any clinical evidence of disease. On 1 January 1977 entry of B and C patients to the study was terminated. Entry of A patients will continue.

Conclusions: Based on the data of all 70 patients entered by all participating institutions it could be concluded that BCG or BCG plus allogeneic tumor cells were unable to prevent recurrences or improve survival in B and C patients. It seems that Stage A patients may benefit from the use of BCG after definitive treatment.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: "Immunological Monitoring and Immunotherapy in Carcinoma of the Lung," R.K. Oldham, et al. The results of this study were presented by Dr. Perlin at the Chicago Symposium on Immunotherapy of Solid Tumors in February 1977, the proceedings of which will also be published. An updated presentation was delivered by Dr. Perlin at the American Society of Clinical Oncology 13th Annual Meeting, Denver, held on 16 and 17 May 1977, and published in the proceedings, page 346. Dr. Herberman of the National Cancer Institute presented data of this study at the Second Conference on Lung Cancer Treatment sponsored by The Division of Cancer Treatment, National Cancer Institute, Airlie House, Virginia on 23 May 1977, in a talk titled "Prospects for Immunotherapy of Lung Cancer with Specific Immunoadjuvants." Proceedings of this meeting will be published in the Cancer Treatment Reports.

Type of Report: Interim

Work Unit No.: 1623

Title of Project: WRMC Protocol 7-00 - Chemoinmunotherapy of Carcinoma of the Large Bowel. Revised December 1976.

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Hein, MAJ, MC
Richard Miskoff, MAJ, MC
Robert Muir, LTC, MC
Salvatore Scialla, MAJ, MC

Objectives: To investigate the therapeutic efficacy of BCG by dermal scarification in patients with carcinoma of the colon or rectum when combined with 5-FU and combination 5-FU and MeCCNU.

Technical Approach:

Patients eligible for this protocol can be put into four broad groups based on the extent of disease:

Type II Patients (Stage B₁) - Extension into but not through muscularis
(Stage B₂) - Extension to or through serosa;
negative nodes

III Patients (Stage C₁) - Limited to serosa; positive nodes
(Stage C₂) - Extension through serosa; positive nodes

IV Patients - Locally metastatic disease beyond lymphatics, the bulk of which can be removed, but with some tumor remaining.

- Cannot tolerate surgery
- Tumor of such size or fixed so that surgery would not be undertaken.

V Patients (Stage D) - Distant metastases

Surgery Protocol - Surgical resection of colon and rectal cancer is undertaken when there are no medical or surgical contraindications and the patient consents to surgery.

Radiotherapy Protocol - "Curative intent" for type IV2 patients
"Palliative intent" for type V patients

Chemotherapy Protocol -

Type II and III - Starting about 3 weeks after surgery, but no later than 6 weeks, or when in the judgement of the physician the patient can tolerate chemotherapy,

these patients will receive 5-FU 10 mg/kg p.o. day 1 through 5 each 28 days. If the first two courses are well tolerated without toxicity, this dose will be increased to 15 mg/kg. Chemotherapy will continue at least 2 years.

Type IV2 - After 2 weeks (10 doses) of radiation, these patients will be treated as V patients.

Type IV1 - About 3 weeks after surgery, these patients will be treated as V patients.

Type IV3 - If after radiotherapy the patient is operable and the tumor is completely resectable, the patient will begin chemotherapy as a type II patient. If the tumor is not completely resectable, they will be treated as type V patients. If after radiotherapy the patient is felt to be inoperable he will be treated as a type V patient.

Type V - Will be treated with combined 5-FU and MeCCNU instead of 5-day 5-FU infusion:
5-FU 325 mg/m² daily I.V. days 1-5 and 36-40 (1 cycle)
MeCCNU 150 mg/m² p.o. day 1

Each cycle is repeated every 10 weeks (day 71).

Immunotherapy Protocol -

Type II and III - Patients randomized to receive BCG will have it administered on days 8, 15, 22 of the chemotherapy cycle for three courses then every 2 weeks (days 8 and 22) thereafter for at least 2 years.

Type IV and V - Patients randomized to receive BCG will have it administered on day 22, 27, 57, etc.

The BCG will be a lyophilized preparation (Phillip Roxane high viability Pasteur BCG). It will be administered as directed on the BCG procedure sheet. For severe local reactions, the next dose of BCG will not be given.

Progress & Results: Seventy-six patients have been entered on study, 6 of whom have no recent follow-up available, 4 are lost to follow-up, one patient was invalid because of carcinoma of the esophagus. Of 23 patients entered for adjuvant treatment, 8 received BCG, 1 of whom has relapsed at 288 days, 7 remain free of disease from 548 to 1279 days. Fifteen patients

no BCG, 2 of these relapsed at 131 and 210 days. Twenty-three patients with metastatic disease received chemotherapy alone, one had a partial remission and subsequent progressive disease at 236 days. Six remain on study from 141 to 463 days with stable disease. The remaining 16 patients had stable disease from 27 to 470 days with subsequent progression. Eight patients with metastatic disease received chemo-immunotherapy. Two remain on study at 619 and 1244 days. Six remained stable with subsequent progression from 93 to 364 days.

Conclusions: Addition of BCG does not add to the response rate or duration of response of patients with metastatic disease, in fact the results of the chemotherapy are rather poor. For the evaluation of the value of adjuvant treatment, the patients will have to be followed for a longer period of time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1629

Title of Project: WRMC Protocol 7407, Add. 3 - Chemoimmunotherapy of Malignant Melanoma

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC
A. Richard Miskoff, MAJ, MC

Objectives: The purpose of this study is to determine if nonspecific immunotherapy with BCG given by dermal scarification is of value in the treatment of malignant melanoma when used after surgery in stage I melanoma and in combination with ICDT (imidazole carboxamide dimethyl triaena) or MeCCNU in stage II-IV melanoma.

Technical Approach:

Patient categories:

- Stage I - No metastatic disease. Primary penetrates beyond the immediate subepidermal zone.
- Stage II - Local recurrence or metastases within 3 cm of the primary. No distant metastases, no lymph node involvement.
- Stage III - Regional metastases more than 3 cm from the primary site.
 - A - Intradermal
 - B - Regional lymph nodes
 - AB - Intradermal and regional nodes. No distant metastases.
- Stage IV - Distant metastases

Treatment schedules:

- Stage I - Within 2 weeks following surgery, the patient will be treated with BCG by dermal scarification weekly for 3 months and then every other week for 21 months.
- Stage II - ICDT 700 mg/m² on day 1 of each 21-day cycle. BCG on day 7, 12 and 17 of the 21-day cycle. This treatment will be continued for at least 2 years after complete remission is achieved until there is evidence of progressive disease.
- Stage III - These patients will be treated as stage II within 2 weeks of surgery. Therapy will continue for at least 2 years or until there is progression of disease.
- Stage IV - As soon as the diagnosis has been established, these patients will receive chemoimmunotherapy as described under stage II. Therapy is continued until there is evidence of disease progression.

Progress & Results: Forty-three patients have been entered, 2 of whom have been lost to follow-up or on whom there is no recent data available. Seventeen patients had Stage I disease, 1 of whom relapsed at day 284 and one at day 315, 15 remain in remission from 22 to 1218 days. Thirteen Stage III patients were entered, seven relapsed from 29 to 694 days, six are remission from 174 to 730 days. Twelve Stage IV patients were entered, 4 remain stable from 125 to 199 days. The remaining 8 patients had progressive disease. The study was closed to entry of new patients on 19 May 1978.

Conclusions: It is too early for conclusions concerning the value of BCG in Stage I melanoma, however in far advanced disease this regimen is minimally active.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1630

Title of Project: WRMC Protocol 7408, Add. 1 - Comparative Trial of
Tamoxifen and Fluoxymesterone plus Tamoxifen in
Metastatic Breast Cancer. (NCI B132)

Investigator:

Principal: Johannes Blom, M.D.

Objectives:

1. Response rates and durations will be compared to assess the relative therapeutic benefit of the two regimens.
2. The quality of survival will be assessed in the two regimens.
3. Prognostic importance of a variety of pretherapy stratification factors will be evaluated.

Technical Approach:

Regimen A - Tamoxifen 2.0 mg/m² p.o. t.i.d.

Regimen B - Fluoxymesterone 7.0 mg/m² p.o. b.i.d.
Tamoxifen 2.0 mg/m² p.o. t.i.d.

The dose of tamoxifen will gradually be increased.

Progress & Results: Thirty six patients have been entered, one of whom is invalid because patient did not take the proper dose and patient was taken off study because receptor studies were negative subsequently. One patient is too early for evaluation. Thirteen had no response or progressive disease. Twenty patients had improvements or stable disease from 70 to 1069 days. Eight of whom are still on study from 34 to 345 days.

Conclusions: Although the response rates are rather low these are all patients who have far advanced carcinoma of the breast and who have not necessarily proven hormone dependency.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1634

Title of Project: WFAMC Protocol 7412, Add. 1 - Metastatic Breast Carcinoma Study to Evaluate the Effect of Cyclophosphamide, Adriamycin and 5-Fluorouracil versus Adriamycin, Dibromodulcitol and Vincristine Sequentially Alternating with Cyclophosphamide, Methotrexate and 5-Fluorouracil. This is a study in cooperation with the National Cancer Institute and the National Naval Medical Center.

Investigator:

Principal: Johannes Blom, M.D.

- Objectives:
1. The response rates obtained with the two induction regimens will be compared for their value as primary induction therapy.
 2. Both programs will be compared for their impact upon response duration.
 3. The prognostic importance of selected pre-therapy stratification factors will be assessed as to their impact upon response rates, response durations and survival within each program.

Technical Approach:

Induction Therapy -

Regimen A - Cytosan 100 mg/m^2 p.o. every day as a single daily dose on days 1-14 of each cycle

Adriamycin 20 mg/m^2 I.V. over 5 minutes on days 1 and 8 of each cycle

5-FU 500 mg/m^2 I.V. push on days 1 and 8 of each cycle

All drugs are recycled to day 1 of the next cycle on day 29 of each cycle, each cycle is 28 days long.

Treatment will be continued for 2 full cycles and thereafter until either patient has progressive disease or no change, at which time they will be removed from protocol, or a total dose of 500 mg/m^2 of adriamycin is obtained after which the patient enters the maintenance phase.

Regimen B - Adriamycin 45 mg/m^2 I.V. day 1 of each cycle

Dibromodulcitol 150 mg/m^2 p.o. every day as a single daily dose on days 1-10 of each cycle

Vincristine 1.2 mg/m^2 I.V. days 1, 8 and 15 of each cycle

Each cycle is 28 days long. This regimen is given for 3 consecutive cycles after which the patient is switched to the following Program:

Cytosan 100 mg/m² p.o. every day as a single daily dose on days 1-14 of each cycle
Methotrexate 40 mg/m² I.V. push on days 1 and 8 of each cycle
5-FU 600 mg/m² I.V. on days 1 and 8 of each cycle

Each cycle is 28 days long. Treatment on this regimen is continued for 3 full cycles after which the patient undergoes sequential therapy with adriamycin, dibromodulcitol, vincristine alternating with cytosan, methotrexate, 5-FU after each 3 cycles until either the patient has progressive disease or no change and is removed from protocol or a total dose of 500 mg/m² of adriamycin is attained after which the patient enters the maintenance phase.

Maintenance Therapy - This is attained after a cumulative dose of 500 mg/m² of adriamycin has been given in both regimens A and B:

Cytosan 100 mg/m² p.o. every day as a single daily dose on days 1-14 of each cycle
Methotrexate 40 mg/m² I.V. push on days 1 and 8 of each cycle
5-FU 600 mg/m² I.V. push on days 1 and 8 of each cycle

Each cycle is 28 days long.

Progress & Results: Twelve patients were entered on the study, Two patients remain in complete remission at 657 and 823 days. The remaining patients obtained an improvement or remained stable until progression from 136 to 837 days. This study was closed to entry of new patients on 31 May 1977.

Conclusions: Based on 90 evaluable patients entered by participating institutions there was no significant difference between responses and duration of response in the two treatment regimens.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: Preliminary results of this study were presented by Dr. Falkson of the University of Pretoria at the 68th Annual Meeting of the American Association of Cancer Research, Denver, Colorado, 1-17 May 1977, page 40 of the published proceedings.

Type of Report: Interim

Work Unit No.: 1643

Title of Project: The Use of Auto Factor IX Concentrate Dried in the Treatment of Patients with Bleeding Due to Factor VIII Inhibitors and the Treatment of Factor VIII Inhibitors.

Investigator: Daniel B. Kimball, Jr., LTC MC

Objectives: To study the usefulness, efficacy and safety of auto-factor IX concentrate in the treatment of inhibitors to factor VIII.

Progress and Results: Since the activation of the study only one patient has presented with bleeding and an inhibitor to factor VIII. She was ineligible for study because of concomitant liver disease.

Conclusions: I desire to keep the study open in order to have the ability to utilize this investigational agent available for the treatment of this difficult management problem.

Funds Utilized, FY-78: None

Funding Requirement, FY-79: None

Publications: None

Type of Report: Interim

Form Unit No.: 1611

Title of Project: WSAAC Protocol 7501 - Evaluation of Adriamycin and Cis-Platinum Combination Chemotherapy in Treatment of Malignant Disease. A Phase II Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: William Babcock, MAJ, MC
Salvatore Scialla, MAJ, MC

Objectives: To evaluate the antitumor activity of the combination of adriamycin and cis-platinum in previously untreated malignancies that have a low order or response to conventional modes of therapy such as head and neck carcinoma, squamous and adenocarcinoma of the lung, metastatic transitional cell carcinoma of the bladder and renal cell carcinoma.

To evaluate the antitumor activity of this combination in malignancies that have become refractory to conventional modes of therapy such as ALL, AML, Hodgkin's disease and non-Hodgkin's lymphoma, oat cell carcinoma of the lung, adenocarcinoma of the prostate, soft tissue sarcoma, and multiple myeloma.

Technical Approach: Adriamycin 60 mg/m^2 I.V. day 1 every 21 days
Cis-platinum 60 mg/m^2 I.V. day 1 every 21 days

Progress & Results: Thirty-one patients with a variety of malignancies have been entered on the study. Eight patients with widespread prostatic carcinoma were entered. 2 expired at day 12 and 15; 2 remain on study with stable disease at 161 and 454 days, the remaining four had stable disease with progression at 172 to 246 days. Minor improvements were seen in carcinoma of the esophagus, adenoid cystic carcinoma of the head and neck area, multiple myeloma and renal cell carcinoma.

Conclusions: None

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1649

Title of Project: WRAMC Protocol 7602, Add. 1 - Chemoinmunotherapy of Prostatic Carcinoma

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC
William McDonald, MAJ, MC
Bernhard Mittenmeyer, COL, MC

Objectives: To study the efficacy of the combination of cyclophosphamide and 5-fluorouracil with and without BCG immunotherapy in the treatment of advanced Stage D carcinoma of the prostate.

Technical Approach:

Regimen A - Cyclophosphamide 1000 mg/m^2 I.V. on day 1
5-fluorouracil 600 mg/m^2 I.V. on days 1 and 8
BCG 6×10^8 units on day 14 and 21

Regimen B - Cyclophosphamide 1000 mg/m^2 I.V. on day 1
5-fluorouracil 600 mg/m^2 I.V. on days 1 and 8

This cycle to be repeated every 28 days.

Progress & Results: WRAMC entered thirteen patients on the study; one patient was not evaluable. Two patients had a partial remission for 176 and 360 days on chemotherapy alone. The remaining seven had stable or progressive disease from 30 to 288 days. One patient on chemotherapy and BCG had a short lived improvement but refused further treatment. Two had progressive disease at 52 and 138 days.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1650

Title of Project: WRMC Protocol 7603 - Evaluation of Galactitol 1,2:
5,6-Dihydro in the Treatment of Advanced Neoplastic
Disease

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the antitumor effect of galactitol in a broad
spectrum of metastatic tumors.

Technical Approach: Galactitol 60 mg/m² I.V. every 7 days

Progress and Results: WRMC entered 21 patients with a variety of tumors,
none of whom had any significant response. Based
on experience by others it seems that further
investigation of this drug is warranted in patients
with resistant carcinoma of the lung and melanoma.
For this purpose this protocol was adapted for a
pilot study for members of the Cancer and Acute
Leukemia Group B. Therefore, WRMC 7603 was closed
for entry of new patients on 30 June 1977.

Conclusions: Galactitol does not seem to be an active agent, but requires
further study in melanoma and carcinoma of the lung.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1651

Title of Project: WRMC Protocol 7604, Add. 1 - Combination Chemotherapy Protocol for the Treatment of Advanced Gastric Carcinoma with either 1-tetra-hydro-2-furanyl-5-fluorouracil (Ftorafur), Adriamycin and Mitomycin-C vs. 5-Fluorouracil, Adriamycin and Mitomycin-C. Addendum 1 eliminated the use of Ftorafur. This is a study in cooperation with the Oncology Service, Georgetown University Hospital.

Investigators:

Principal: Johannes Blom, M.D.

Associate: J. Phillip Olmert, MAJ, MC

Objectives: To study the efficacy of and compare the results of treatment with Ftorafur, adriamycin, and mitomycin-C with 5-fluorouracil, adriamycin and mitomycin-C.

Technical Approach: Ftorafur 1500 mg/m² I.V. daily for 5 days during week 1 and 5 of each 8 week cycle
Adriamycin 30 mg/m² I.V. on day 1 and day 29
Mitomycin-C 10 mg/m² I.V. on day 1 of each 8-week cycle

5-fluorouracil 600 mg/m² I.V. on days 1 and 8 and days 29 and 36 of each 8-week cycle
Adriamycin 30 mg/m² I.V. on days 1 and 29 of each 8-week cycle
Mitomycin-C 10 mg/m² I.V. on day 1 of each 8-week cycle

Regimen I with ftorafur was discontinued on 1 July 1977.

Progress & Results: WRMC entered 14 patients, one patient was never begun on treatment, four are not evaluable. Two patients on ftorafur had progressive disease by day 44 and 208. One developed congestive heart failure by day 386 and expired on day 557. Six patients were treated with regimen II. One had complete regression of liver metastases with recurrence by day 200, one had a short partial remission, the remaining four had progressive disease from 37 to 441 days.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: Presentation 13th Annual meeting of American Society of
Clinical Oncology May 1977.

Type of Report: Interim

Task Unit No.: 1652

Title of Project: WRAMC Protocol 7605 - Combination Chemotherapy Chemotherapy of Advanced Pancreatic Carcinoma with 5-Fluorouracil, Mitomycin-C and Streptozotocin. This is a study in cooperation with the Oncology Service, Georgetown University Hospital.

Investigators:

Principal: Johannes Blom, M.D.

Associate: J. Phillip Olmert, MAJ, MC

Objectives: To examine the efficacy of the combination of three active single agents, 5-fluorouracil, mitomycin-C and streptozotocin, in advanced pancreatic carcinoma.

Technical Approach: 5-fluorouracil 15 mg/kg I.V. weekly plus Streptozotocin 1 gm/m^2 I.V. weekly plus Mitomycin-C 10 mg/m^2 I.V. every 6 weeks
Entry of patients on this regimen was closed on 1 July 1977 and all patients were treated with 5-fluorouracil, adriamycin, mitomycin-C, according to protocol 7604.

Progress & Results: WRAMC has entered 17 patients. One patient was not evaluable because patient refused further therapy. One patient is too early and no recent information on two patients. One patient had a complete remission for 300 days and one a partial remission for 391 days. The remaining eleven patients stable or progressive disease from 35 to 255 days.

Funding Requirements: See introductory remarks to Annual Research Report.

Publicatons: None

Type of Report: Interim

Work Unit No.: 1675

Title of Project: WRAMC Protocol 7616 - Phase I-II Study of High Dose Methotrexate (MTX) with Citrovorum Factor Rescue for Children and Adults with Metastatic Osteosarcoma and Advanced Gliomas of the Brain.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Alan D. Wease, MAJ, MC
Frederick B. Ruyman, LTC, MC

Objectives: To evaluate the efficacy and kinetics of high dose methotrexate in the treatment of malignant neoplasms in adults and children.

Technical Approach: Vincristine 2 mg/m^2 ; maximum dose 2 mg, to be followed by Methotrexate infusion in doses varying from 100-500 mg/kg I.V. over 6 hours and followed by Citrovorum rescue 15 mg/m^2 I.V. every 6 hours for 12 doses beginning 2 hours after completion of the methotrexate infusion.

Progress & Results: WRAMC entered five patients, one with the extra-osseous Ewings sarcoma who was not evaluable. One with osteosarcoma had stable disease for 300 days. One osteosarcoma, one osteochondrosarcoma and one rhabdomyosarcoma had progressive disease.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit I.

Title of Project: NCI Protocol 7601-A, Add. 1 - The Treatment of Unresectable Bronchogenic Carcinoma with CCNU (1-(2-Chloroethyl)-3-Cyclohexyl-1-Nitrosourea)(NSC 79037), Cyclophosphamide, Adriamycin, Procarbazine, Hexamethylmelamine (NSC 13875), Methotrexate and Irradiation

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the efficacy of combination chemotherapy with CCNU, cyclophosphamide, adriamycin, procarbazine, hexamethylmelamine and methotrexate and radiotherapy in remission induction and prolongation and survival of patients with unresectable bronchogenic carcinoma.

Technical Approach:

No prior chemotherapy or radiotherapy:

CCNU 65 mg/m² p.o. day 1 each 56 days
Cytosan 500 mg/m² I.V. push day 1 each 56 days
Adriamycin 30 mg/m² I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 100 mg/m² p.o. days 8 to 18 each 56 days
Methotrexate 40 mg/m² I.V. push on day 50 each 56 days

Prior chemotherapy or radiotherapy:

It must be at least 3 weeks since the last dose of prior chemotherapy or 2 weeks from the last dose of radiation before patients are started on this protocol. For these patients, the first and second course of therapy will be:

CCNU 35 mg/m² p.o. day 1 each 56 days
Cytosan 250 mg/m² I.V. push day 1 each 56 days
Adriamycin 15 mg/m² I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 50 mg/m² p.o. days 8 to 18 each 56 days
Methotrexate 20 mg/m² I.V. push day 50 each 56 days

If this dose is tolerated without a nadir WBC of less than 2500 or a nadir platelet count of less than 75,000, the third and fourth courses will be given in the following doses:

CCNU 50 mg/m² p.o. day 1 each 56 days
Cytovan 375 mg/m² I.V. push day 1 each 56 days
Adriamycin 25 mg/m² I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 75 mg/m² p.o. days 3 to 18 each 56 days
Methotrexate 30 mg/m² I.V. push day 50 each 56 days

If these four courses are well tolerated by the above criteria, full doses will be given subsequently.

Progress & Results: WRAMC entered 37 patients, one of whom was never begun on treatment. Six patients received less than one full cycle of treatment. Three patients had a complete remission and five a partial remission. Twenty-one patients had minimal or no response at all. The median survival of the responders was 377 days and of the non responders 146 days. Six patients are still alive, two of whom continue in complete remission at 450 and 517 days. This study was closed to entry of new patients on 31 May 1977.

Conclusions: Response rate of approximately 25% is not significantly dissimilar from response rates with less intense chemotherapeutic programs. Further entry of patients is, therefore, not warranted.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: A manuscript has been submitted.

Type of Report: Interim

Work Unit No.: 1655

Title of Project: WRAMC Protocol 7607 - Chemoimmunotherapy of Carcinoma of the Lung using High-Dose Methotrexate and Citrovorum Factor with or without BCG. This is a study in cooperation with the National Cancer Institute and Bethesda National Naval Medical Center.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC

- Objectives:
1. To evaluate the response obtained with high dose methotrexate plus citrovorum factor rescue and radiation therapy in patients with residual carcinoma of the lung restricted to the thorax.
 2. To evaluate the effect of BCG immunotherapy both in regard to clinical response to high dose methotrexate and also to immunologic function.
 3. To have this investigation function as a pilot study for eventual use of chemoimmunotherapy as an adjuvant therapy regimen in patients with no residual tumor at the time of operation.

Technical Approach:

Regimen A - High dose methotrexate to begin with 17 mg/kg I.V. over 6 hours, followed by calcium leucovorin rescue 9 mg every 6 hours for a total of 12 doses. Doses of methotrexate will be increased to 50 mg/kg, 100 mg/kg, 200 mg/kg and 300 mg/kg. Subsequent to this radiation therapy 1500 rads will be given to large ports including the resected area and the mediastinum. Subsequent to this courses of high dose methotrexate will be continued.

Regimen B - Consists of the same high-dose methotrexate plus BCG.

Progress & Results: WRAMC has entered seven patients. One patient with extensive neuroblastoma had progressive disease on day 15. One patient has stable disease at day 361. Five patients had stable or progressive disease from 30 to 120 days.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1696

Title of Project: WRAMC Protocol 7603 - The Use of Thymosin (F5) in Patients with Carcinoma of the Esophagus. A Phase I Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC
Howard Heit, MAJ, MC
Lawrence Johnson, LTC, MC

- Objectives:
1. To determine if doses of thymosin that have not been toxic thus far in patients with solid malignancies are toxic when given in combination with radiation therapy.
 2. To determine if thymosin alters the progressive decline in peripheral blood T cells that occurs in patients receiving radiation therapy.
 3. To determine if thymosin improves the clinical response of patients receiving radiation therapy.
 4. To determine if thymosin affects the disease-free interval and survival when used as an adjuvant to radiation therapy.

Technical Approach: All patients will receive conventional radiation therapy to a total tumor dose of 5000 rads via opposed anterior and posterior fields covering the width of the mediastinum and the ipsilateral supra-clavicular area on all patients. Patients will be assigned randomly to receive low dose thymosin 20 mg/m², high dose thymosin 60 mg/m² or placebo daily during the entire period of radiation therapy. This is a study in cooperation with the National Cancer Institute.

Progress & Results: WRAMC has entered one patient who was a control. Because of lack of sufficient number of patients in all participating institutions, the study was closed 13 February 1978

Conclusions: None

Publications: None

Type of Report: Final

Work Unit No.: 1659

Title of Project: WRAMC PROTOCOL # 7703: Hepatic Artery Infusion with 5-Fluorouracil.

Investigators:

Principal: Johannes Blom, M.D.

Associates: Patrick Farley, M.D.
Robert Muir, M.D.
Salvatore Scialla, M.D.

Objectives: To study incidence of response of hepatic metastatic disease to this form of therapy as opposed to other forms of systemic therapy.

Provide palliation and prolonged survival to this patient group.

Technical Approach: Angiographic study of the vascular anatomy and placement of the catheter (s) will be performed by the special procedures team. Transbrachial catheterization is preferred over the transfemoral approach. At least weekly, and where otherwise indicated, the catheter position should be confirmed angiographically.

Dilute 5-FU in appropriate volume of infusage and continue on 24-hour perfusion for preferably 21 days.

Suggested dosage: 5-FU 20 mg/kg/24 hours x 4 days,
subsequently 5-FU 15 mg/kg/24 hours x 17 days.

Progress & Results: Five patients have been entered. One patient had a hepatoma, had only a 10 day infusion with minimal improvement, she expired six weeks later. One patient had a cholangiohepatoma. She had a 20 day course with no change. She was subsequently begun on systemic therapy. One patient had well differentiated adenocarcinoma of the rectum with hepatic metastases. She had one 11 day course and one 19 day course with improvement, patient expired. One patient had hepatic metastases of carcinoma of the breast. She had a 12 day course when she developed mouth ulcers, diarrhea, leukopenia and thrombocytopenia. The catheter was found to have slipped. Patient had improvement of liver functions and decrease in size of liver. She expired two months later.

One patient had hepatic metastases, probably from pancreas. He had a 15 day infusion with slight decrease of liver size and stable liver functions. He was subsequently begun on systemic therapy.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1661

Title of Project: Polycythemia Vera Study Group (PVSG) Protocols

Investigators:

Principal: Daniel B. Kimball, Jr., LTC, MC

Associate: Staff and Fellows of Hematology/Oncology Service

Objectives: To study therapeutic modalities and natural history of several myeloproliferative diseases.

Technical Approach: See details of each protocol listed in Progress & Results Section.

Progress & Results: In FY 1978, WRAMC followed 3 patients registered on PVSG Protocols. (Protocol 01, Protocol 05 and Protocol 09).

Protocol 01 was never submitted to CIS for approval having been closed to patient entry in 1973. Mrs. E J was randomized to P32 and phlebotomy for Polycythemia Vera at Fort Bragg, North Carolina in 1970 and continues to be followed on the protocol. She continues to do very well with 100% performance score. Nationally, 426 patients were randomized to receive phlebotomy alone, P32 plus phlebotomy, or chlorambucil + phlebotomy therapy for polycythemia vera. At last analysis (May 1978) the over-all mortality rate was 21% with a median follow-up of 3.5 years (Phlebotomy - 19%, Chlorambucil - 24% and P32 - 20%). Definitely alive was 37% of the over-all group (phlebotomy - 32%, chlorambucil - 37% and P32 - 42%) with a significant 43% of the group pending or lost to follow-up. The mortality and survival figures do not show significantly different therapeutic effects but with regard to thrombotic events and second neoplasms patients on P32 are at a significantly lowered risk of a therapeutic failure than patients on phlebotomy ($P = 0.002$) or chlorambucil ($P = 0.06$).

A Phase III Randomized trial of Myeloproliferative Disorders comparing Androgen Therapies for low red cell production; splenectomy vs Alkeran for complications of splenomegaly; P32 vs Alkeran for the treatment of Primary Thrombocytosis was submitted to CIS and approved during 1977. This entire protocol was originally identified as Protocol 04 but at the May 1978 meeting was redesignated as three separate protocols (Protocols 09, 10 and 11).

Protocol 09 is now titled "Phase III Randomized trial comparing splenectomy vs P32 vs Alkeran for the complications of splenomegaly in myeloproliferative disorders". Protocol 10 is now titled "Phase III Randomized trial comparing P32 vs Alkeran and persantine plus aspirin vs placebo in the treatment of myeloproliferative disorders". Protocol 11 is now titled "Phase III Randomized trial comparing High Dose Oral vs High Dose Intramuscular Antrogens in the treatment of the Anemias".

Ms. R B was originally randomized to Protocol 04 in 1977 and is currently listed by the PVSG Central Office as being on Protocol 10. She was randomized to Alkeran therapy with an initial partial response and more recently a complete response with a current performance rating of 90%. Thirty-six patients are randomized nationally and no significant differences can be detected between the Alkeran and P32 groups. The most recent data analysis is attached (May 1978).

Ms. N B was randomized to Protocol 05 in November 1977 to receive persantine and aspirin plus phlebotomy for her polycythemia rubra vera. Persantine was discontinued temporarily in February 1978 and permanently in August 1978 due to recurrent skin rash. The patient continues mildly symptomatic (performance score 80%) in a partial remission. Forty-four patients have been randomized nationally to this study with insufficient data to date for analysis.

A list of the current PVSG protocols is attached.

Protocols 02, 03 and 12 have never been submitted.

No patients have been entered on Protocols 06, 07, 08, 09 or 11.

Conclusions: Protocol 01 is closed to patient entry and follow-up continues. Protocol 05 - 11 continue.

Funding Requirements: Funding for PI and one fellow to attend twice yearly two day meeting in New York City.

Publications: None

Type of Report: Interim

POLYCYTHEMIA VERA STUDY GROUP

List of Protocols

Protocol No.	Protocol Title	Status
01	Phase III Randomized Trial comparing ³² P vs Chlorambucil vs Phlebotomy Alone in the Treatment of Polycythemia Vera	Ongoing (Patient entry closed)
02	Phase II Efficacy Trial comparing Alkeran vs Leukeran in the Treatment of Polycythemia Vera	Completed
03	Phase II Efficacy Trial using Azaribine in Treatment of Polycythemia Vera	Discontinued
04	Phase III Randomized Trial of Myeloproliferative Disorders comparing Androgen Therapies for Low Red Cell Production; Splenectomy vs Alkeran for Complications of Splenomegaly; ³² P vs Alkeran for the Treatment of Primary Thrombocytosis	Closed (see Protocols #09, 10, 11)
05	Phase III Randomized Trial comparing ³² P vs Phlebotomy plus Deaggregating Agents for the Prevention of Thrombosis in Polycythemia Vera	Active
06	Phase II Efficacy Trial for the Treatment of Acute Leukemia preceded by Polycythemia Vera	Active
07	Phase II Efficacy Trial using Potaba in the Treatment of Post-Polycythemic and Agnogenic Myeloid Metaplasia	Active
08	Phase II Efficacy Trial using Hydroxyurea in the Treatment of Polycythemia Vera	Active
09	Phase III Randomized Trial comparing Splenectomy vs ³² P vs Alkeran for the complications of Splenomegaly in Myeloproliferative Disorders	Active
10	Phase III Randomized Trial comparing ³² P vs Alkeran and Persantine plus Aspirin vs Placebo in the Treatment of Myeloproliferative Disorders	Active
11	Phase III Randomized Trial comparing High Dose Oral vs High Dose Intramuscular Androgens in the Treatment of the Anemias	Active
12	Phase II Efficacy Trial using Hydroxyurea in the Treatment of Thrombocytosis	Active

Table P1

Comparison of Alkeran and ³²P
Patients with Primary Thrombocytosis -
Initial Characteristics - PVSG-C4

<u>Characteristic:</u>	<u>³²P</u>		<u>Treatment</u>		<u>Total</u>	
			<u>Alkeran</u>			
	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
Number in Group	19	100.0	17	100.0	36	100.0
Ht:Wt ≤.5	13	68.4	12	70.6	25	69.4
>.5	6	31.6	5	29.4	11	30.6
Age <50	3	15.8	10	58.8	13	36.1
50-70	11	57.9	6	35.3	17	47.2
≥70	5	26.3	1	5.9	6	16.7
Pathologists Diagnosis						
Thrombocytosis	15	78.9	14	82.4	29	80.6
Unclassified MPS	0	0.0	1	5.9	1	2.8
Other	0	0.0	1	5.9	1	2.8
Unknown	4	21.1	1	5.9	5	13.9
Splenomegaly						
No	13	68.4	8	47.1	21	58.3
Yes	6	31.6	9	52.9	15	41.7
Hgb ≤10	4	21.1	3	17.6	7	19.4
10-15	14	73.7	8	47.1	22	61.1
>15	1	5.3	5	29.4	6	16.7
Missing	0	-	1	5.9	1	2.8
Retics ≤1.0	10	52.6	9	52.9	19	52.8
1.0-2.0	6	31.6	2	11.8	8	22.2
>2.0	3	15.8	5	29.4	8	22.2
Missing	0	-	1	5.9	1	2.8
Plasma Vol ≤40	3	15.8	2	11.8	5	13.9
40-50	10	52.7	7	41.2	17	47.2
>50	6	31.6	8	47.1	14	38.9
Performance Status						
≤ 70	1	5.3	3	17.6	4	11.1
80	7	36.8	4	23.5	11	30.6
90	6	31.6	4	23.5	10	27.8
100	5	26.3	5	29.4	10	27.8
Missing	0	-	1	5.9	1	2.8
Prior Stroke No	17	89.4	15	88.2	32	88.9
Yes	2	10.6	2	11.8	4	11.1
Prior Thrombosis No	14	73.7	13	76.5	27	75.0
Yes	5	26.3	4	23.5	9	25.0

POLYCYTHEMIA VERA STUDY GROUP

List of Protocols

Protocol No.	Protocol Title	Status
01	Phase III Randomized Trial comparing ³² P vs Chlorambucil vs Phlebotomy Alone in the Treatment of Polycythemia Vera	Ongoing (Patient entry closed)
02	Phase II Efficacy Trial comparing Alkeran vs Leukeran in the Treatment of Polycythemia Vera	Completed
03	Phase II Efficacy Trial using Azaribine in Treatment of Polycythemia Vera	Discontinued
04	Phase III Randomized Trial of Myeloproliferative Disorders comparing Androgen Therapies for Low Red Cell Production; Splenectomy vs Alkeran for Complications of Splenomegaly; ³² P vs Alkeran for the Treatment of Primary Thrombocytosis	Closed (see Protocols #09, 10, 11)
05	Phase III Randomized Trial comparing ³² P vs Phlebotomy plus Deaggregating Agents for the Prevention of Thrombosis in Polycythemia Vera	Active
06	Phase II Efficacy Trial for the Treatment of Acute Leukemia preceded by Polycythemia Vera	Active
07	Phase II Efficacy Trial using Potaba in the Treatment of Post-Polycythemic and Agnogenic Myeloid Metaplasia	Active
08	Phase II Efficacy Trial using Hydroxyurea in the Treatment of Polycythemia Vera	Active
09	Phase III Randomized Trial comparing Splenectomy vs ³² P vs Alkeran for the complications of Splenomegaly in Myeloproliferative Disorders	Active
10	Phase III Randomized Trial comparing ³² P vs Alkeran and Persantine plus Aspirin vs Placebo in the Treatment of Myeloproliferative Disorders	Active
11	Phase III Randomized Trial comparing High Dose Oral vs High Dose Intramuscular Androgens in the Treatment of the Anemias	Active
12	Phase II Efficacy Trial using Hydroxyurea in the Treatment of Thrombocytosis	Active

(cont) Comparison of Alkeran and 32p

		<u>32p</u>		<u>Alkeran</u>		<u>Total</u>	
		<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
Prev. phlebotomy	No	19	100.0	17	100.0	36	100.0
	Yes	0	-	0	-	0	-
Prior hemorrhage	No	13	68.4	8	47.1	21	58.3
	Yes	6	31.6	9	52.9	15	41.7
Pruritus	No	17	89.4	14	82.4	31	86.1
	Yes	2	10.6	3	17.6	5	13.9
Dizziness	No	15	78.9	12	70.6	27	75.0
	Yes	4	21.1	5	29.4	9	25.0
Vision abnormality							
	No	12	63.2	12	70.6	24	66.7
	Yes	7	36.8	5	29.4	12	33.3
Weakness	No	11	57.9	7	41.2	18	50.0
	Yes	8	42.1	10	58.8	18	50.0
Weight loss	No	13	68.4	11	64.7	24	66.7
	Yes	6	31.6	6	35.3	12	33.3
RBC morphology							
	Normal	2	10.5	0	-	2	5.6
	Abnormal	0	-	1	5.9	1	2.8
	Missing	17	89.5	16	94.1	33	91.7
Sex							
	Male	9	47.4	6	35.3	15	41.7
	Female	10	52.6	11	64.7	21	58.3
Cytogenetics							
Summary Code							
	Normal	6	31.5	5	29.4	11	30.5
	Possibly or	-	-	-	-	-	-
	Definitely Abnormal	-	-	-	-	-	-
	Missing	13	68.5	12	70.6	25	69.5
Cellularity							
	Normal	3	15.8	0	0.0	3	8.3
	Sl. hypocellular	1	5.3	0	0.0	1	2.8
	Sl. hypercellular	1	5.3	3	17.6	4	11.1
	Mod. hypercellular	10	52.6	12	70.6	22	61.1
	Marked hypercellular	0	-	1	5.9	1	2.8
	Missing	4	21.1	1	5.9	5	13.9
Serum B12							
	<300	2	10.5	1	5.9	3	8.3
	300-600	4	21.1	3	17.6	7	19.4
	>600	9	47.4	8	47.1	17	47.2
	Missing	4	21.1	5	29.4	9	25.0

(cont) Comparison of Alkeran and 32p

	<u>32p</u>		<u>Alkeran</u>		<u>Total</u>	
	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
Plasma Iron						
≤80	9	47.4	5	29.4	14	38.9
80-120	7	36.8	6	35.3	13	36.1
>120	3	15.8	4	23.5	7	19.4
Missing	0	-	2	11.8	2	5.6
Serum Folate						
≤5	3	15.8	6	35.3	9	25.0
5-10	9	47.4	2	11.8	11	30.6
>10	1	5.3	2	11.8	3	8.3
Missing	6	31.6	7	41.2	13	36.1

PVSG
9/78

Table P2

Survival of Patients with
Primary Thrombocytosis PVSG-04
by Treatment Group

<u>Status</u>	<u>Treatment Group</u>			
	<u>32p</u>		<u>Alkeran</u>	
	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
Dead	2	10.5	3	17.6
Censored	17	89.5	14	82.4
Total	19	100.0	17	100.0
Maximum Weeks on Study	172		188	

PVSG
9/78

Table P3

Response by Treatment Group
Patients with Primary Thrombocytosis - PVSG-04

<u>Three Month Response</u>	<u>32p</u>		<u>Treatment</u>		<u>Total</u>	
	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
No	10	52.6	7	41.2	17	47.2
Yes	7	36.8	8	47.1	15	41.7
Unknown	2	10.5	2	11.8	4	11.1
Total	19	100.0	17	100.0	36	100.00

Six Month Response

	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>	<u>#</u>	<u>%</u>
No	12	63.2	4	23.5	16	44.4
Yes	4	21.1	8	47.1	12	33.3
Unknown	3	15.8	5	29.4	8	22.2
Total	19	100.0	17	100.0	36	100.0

PVSG
9/78

Table P4

Primary Thrombocytosis - PVSG04
 Known Response* Status at 6 Months
 by Treatment Group and Initial Characteristics

Characteristics	Treatment Group									
	³² P Response					Alkeran Response				
	No #	%	Yes #	%	Total #	No #	%	Yes #	%	Total #
Total	12	75.0	4	25.0	16	4	25.0	8	75.0	12
Age										
<50	2	67.7	1	33.3	3	1	14.3	6	85.7	7
50-70	8	88.9	1	11.1	9	3	75.0	1	25.0	4
> 70	2	50.0	2	50.0	4	0	-	1	100.0	1
Splenomegaly										
No	6	60.0	4	40.0	10	0	-	4	100.0	4
Yes	6	100.0	0	-	6	4	50.0	4	50.0	8
Sex Male	8	100.0	0	-	8	2	40.0	3	60.0	5
Female	4	50.0	4	50.0	8	2	28.6	5	71.4	7
Vision Abnormalities										
No	8	80.0	2	20.0	10	4	40.0	6	60.0	10
Yes	4	67.7	2	33.3	6	0	-	2	100.0	2
Weakness										
No	8	88.9	1	11.1	9	2	33.3	4	67.7	6
Yes	4	57.1	3	42.9	7	2	33.3	4	67.7	6

* Platelets \leq 400,000

Table P5

Platelets $\times 10^3$ at 6 Months by Age at IE and
Treatment Group*
Primary Thrombocytosis - PVSG-04

<u>Age at IE</u>		<u>Treatment Group</u>	
		<u>^{32}P</u>	<u>Alkeran</u>
<50	#	3	7
	mean	371.7	342.3
	s.e.	106.7	77.3
50-70	#	9	4
	mean	583.9	415.3
	s.e.	67.7	19.0
>70	#	4	1
	mean	570.8	242.0
	s.e.	291.2	-

*Patients with known platelets at 6 months.

Work Unit No.: 1662

Title of Project: WRAMC Protocol # 7704, Chlorozotocin in Metastatic Malignant Melanoma Resistant to ICDT.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Jeffrey L. Berenberg, M.D.

Objectives: To determine the efficacy of chlorozotocin in metastatic malignant melanoma resistant to treatment with ICDT or Combinations with ICDT.

Technical Approach: Treatment schedule/Dose modifications:

Chlorozotocin 120 mg/m^2 IV every 6 weeks

WBC < 2500 or platelets $< 75,000$, reduce to 80 mg/m^2

Escalate dose to 150 mg/m^2 after 2 courses of 120 mg/m^2 if no evidence of leukopenia or thrombocytopenia

Progress & Results: One patient was entered who had progressive disease. Because of activation of a study with chlorozotocin in the CALGB, the study was closed. This is the final report.

Conclusions: Too early

Funding Requirements: , See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit Number: 1663

Title: A Phase II Trial of Galacticol 2,2:5,6-Dianhydro in Patients with Advanced Pelvic Malignancies

*Investigators: Robert C. Park, COL, MC, USA, Chief, OB-GYN Dept, WRAMC
Johannes Blom, M.D., Department of Medical Oncology, WRAMC*

Objective: To ascertain if Galacticol has anti-tumor activity in patients with advanced pelvic malignancies who are not eligible for more standard treatment.

Technical Approach: Patients with radiation recurrence of carcinoma of the endometrium and cervix who are not amenable to surgical cure or established chemotherapeutic agents are eligible.

Progress and Results: This is a Gynecologic Oncology Group study. This study has terminated. Walter Reed placed five patients with carcinoma of the cervix, recurrent, and one patient with carcinoma of the endometrium, recurrent. In the five Walter Reed patients, there were no responses noted. In addition, there was no serious toxicity. In the entire GOG group of patients, there was a 20% response rate to this drug for recurrent squamous cell carcinoma of the cervix.

Conclusions: Galacticol may have minimal activity in patients with recurrent carcinoma of the cervix. Further trials are justified particularly in combination with other known active drugs.

Funds Utilized, FY-78: No military funds were expended. This was a GOG funded project.

Funding Requested, FY-79: No funding requested for 79.

Publications, FY-78: No publications in 78. A GOG report is being formulated for 79.

Type of Report: This study has been completed.

Work Unit No.: 1701

Title of Project: Phagocyte Chemotaxis in Patients with Bronchogenic Carcinoma.

Investigators:

Principal: K. Kellogg Hunt, LTC MC
Chief, Pulmonary Service
Department of Medicine, WRAMC

Coinvestigator: Carlos C. Daughaday, MAJ MC
Department of Hematology
Division of Medicine, WRAIR

Objectives: a) To study monocyte chemotaxis in patients with bronchogenic carcinoma and to determine if defects in chemotaxis have any relationship to histologic type of tumor, stage of disease, complications, or clinical course. b) To determine if in vitro treatment with Levamisole can reconstitute normal chemotactic activity.

Type of Report: Termination.

Work Unit No: #1702

Title of Project: Effect of Unilateral Major Airway Obstruction On Maximal Expiratory Flow Volume Loop

Investigators: Robert G. Hooper, M.D.
LTC, MC
Chief, Pulmonary Function Laboratory

Objectives: The objectives of this study was to evaluate the effect of unilateral endobronchial obstruction on the maximum expiratory flow volume curve.

Technical Approach: A two lung model was used to evaluate the contribution of expiratory flow and volume. Flow, volume, and time were measured simultaneously with each lung model emptying independently and with system emptying as a unit. To evaluate the contribution of individually emptying lung units, the expiratory flow of each individual lung unit was plotted against the expiratory time axis for the total system. The sum of these flows from each model lung unit was then compared with the flow for the total system.

Progress & Results: Studies have been completed as of this time and preliminary reports published.

Conclusions: This study demonstrated that two major factors contribute to expiratory air flow and the maximum expiratory flow volume curve of patients with endobronchial airway obstruction. These two major factors are the effect of flow addition in the major airways and asynchronous emptying of the lung units.

Funds Utilized, FY 78: None

Funding Requested, FY 79: None

Publications, FY 78: 1. Hooper, RG: Expiratory flow volume abnormalities with major airway obstruction - A model lung study. Clinical Research 26:448A, April 1978. (Abstract)

2. Hooper, RG, Tellis, CJ: Major airway obstruction and the flow volume relationship. XIII World Congress on Disease of the Chest, Kyoto, Japan. July 1978 (Abstract-Presentation)

3. Papers are in preparation at this time and will be submitted when completed.

Type of Report: Completed

1. Work Unit No.: 1801
2. Title of Project: Direct Immunofluorescence in MCTD
3. Investigators:
 - a. Principal: ROBERT A. DAVIS, MAJ, MC, USA
 - b. None
4. Objectives: (Goal of Research)

To determine the immunofluorescence pattern in mixed connective tissue disease and its relationship to lupus erythematosus, scleroderma and dermatomyositis and attempt to correlate the immunofluorescence with the ENA titers in these patients.
5. Technical Approach: Perform 4 mm punch biopsies of skin on patients suspected of having mixed connective tissue disease. Direct immunofluorescent tests were performed on these biopsies and examined for any abnormal fluorescence, specifically looking at the dermal epidermal junction and looking at the nuclei of epidermal cells.
6. Progress and Results: Between 1 July 1977 and 30 June 1978, 141 biopsies were submitted to dermatology for examination for immunofluorescence. Biopsies were examined for evidence of immunofluorescence in MCTD and in many other skin diseases. Biopsy specimens were submitted with the following tentative diagnoses: Discoid and systemic lupus erythematosus, dermatitis herpetiformis, herpes gestationis, mixed connective tissue disease, scleroderma, dermatomyositis, erythema multiforme, drug eruption, vasculitis, angioedema, pemphigoid, pemphigus, chronic oral ulceration, lichen planus, urticaria, erythromelalgia, polymorphous light eruption, porphyria, scarring alopecia and erythema dyschromicum perstans. Thirty-two of the 141 biopsy specimens were positive at the dermal epidermal junction. Twenty-three of the 32 positive specimens were from involved skin and nine were from uninvolved skin. Of the 32 positive staining specimens at the dermal epidermal junction, 20 were from patients with DLE or SLE; 4 were from patients with MCTD; 2 were from patients with bullous pemphigoid; 4 were from patients with dermatitis herpetiformis; 1 was from a patient with palpable purpura; and 1 was from a patient with subcorneal pustular dermatoses. Four patients were suspected of having MCTD. Of the 4 patients examined for MCTD 3 had specimens of uninvolved skin examined and all 3 were positive at the dermal epidermal junction. One patient had only involved skin examined and it was negative. Two of the 3 patients had ENA titers performed and their titers were low. None of the 4 had in vivo staining of epidermal nuclei. One patient with a diagnosis of SLE had positive staining of the DE junction in addition to positive in vivo staining of epidermal nuclei. This patient was also on Plaquinal 600 mg p.o., q.i.d. ENA titers are not available on this patient. In addition to the above studies, 4 serum samples were examined with indirect immunofluorescence to rule out pemphigus and pemphigoid. All 4 specimens were negative. Also, 2 blood samples were examined for evidence of red blood cell fluorescence to rule out porphyria cutanea tarda. Both specimens were negative.

7. The fact that the patients with a diagnosis of MCTD had low titers of ENA and had no in vivo staining of epidermal nuclei supports the fact that possibly only patients with high ENA titers may have positive in vivo staining of epidermal nuclei. More patients with MCTD will be examined over the next few years, especially as the ENA test becomes more readily available.

8. Funds Utilized - FY 78:

a. Personnel:	ROBERT A. DAVIS, MAJ, MC
b. Equipment:	None
c. Supplies:	\$1,187.00
d. Travel:	None
e. Other:	None
f. Funds not utilized:	\$290

9. Funds Requested - FY 79

a. Personnel:	ROBERT A. DAVIS, MAJ, MC
b. Equipment:	None
c. Supplies:	Immunologic reagents, glassware and miscellaneous Items - \$800.00
d. Travel:	None
e. Other:	None

10. Publications: None

11. Type of Report: Interim

Unit No.: 1901

Title of Project: The Efficacy of Antisera to Gram Negative Endotoxin in the Treatment of Gram Negative Sepsis

Investigators:

Principal: Jerald Sadoff, M.D.

Associate: John B. McClain, M.D.

Objective: To evaluate the efficacy of antisera which is made against a "common antigen" in the core of the endotoxin of gram negative rods in treating suspected or documented gram negative sepsis.

Technical Approach: Patients with documented or suspected gram negative sepsis were given antisera in addition to standard antibiotic and supportive therapy. The antisera were administered in a double blind fashion in that two units had been prepared from each donor; one obtained pre-immunization and one post-immunization. An individual patient would receive either the pre or post-immunization sera. The patients were clinically evaluated pre and post therapy by the investigators and the data recorded on standard flow sheets. This clinical information was then relayed to Dr. Elizabeth Ziegler at the University of California at San Diego, who is coordinating this multi-center study.

Progress and Results: During FY 78, 9 units of antisera were given without significant complications. The efficacy of the antisera has not been determined as the code in this double blind study has not yet been broken.

Laboratory Studies: Approximately 108 solid phase radioimmunoassays were performed investigating.

1. The cross reactivity of sera from J-5 immunized rabbits to a series of mutant LPS which progress from naked lipid A through various carbohydrate residues to a full O-side chain.
2. The cross reactivity of sera from J-5 immunized rabbits to various strains of gonococcus, meningococcus, pseudomonas, and other gram-negative organisms.
3. The amount of antibody to J-5 LPS in pre- and postimmunization sera from subjects immunized with J-5 organisms.

27 hemagglutinations were performed investigating the titre of antibody to J-5 in various sera from patients, immunized subjects and rabbits.

The conclusion from the above studies

1. There is a moderate amount of cross-reactivity between J-5 antibody and the LPS's from mutants two sugar residues in and out from the J-5 LPS.
2. There is a low level of cross reacting antibodies between J-5 and other species of gram negative organisms with one or two exceptions.
3. The amount of antibody rise between pre- and postimmunization humans is very small on RIA and not detectible with hemagglutination techniques.
4. There are substantial amounts of naturally occurring J-5 antibodies in the human prior to immunization.
5. There are only small amounts of RE antibodies elicited by sepsis with other organism.

Conclusions: Deferred at present.

Funds Utilized, FY 78: \$3,500.

Funding Requirements, FY 79: \$6,000.

Publications: None.

Type of Report: Interim - Annual Progress Report

Work Unit No.: 1903

Title of Project: Persistence of T. Pallidum in Neurosyphilis

Investigators:

Principal Investigator: Edmund C. Tramont, LTC MC

Objective: To determine the frequency with which Treponema pallidum can be isolated from the cerebrospinal fluid (CSF) of patients who have received recommended course of treatment for 1 or 2 syphilis, and to examine the CSF of these patients to determine whether improved procedures for detecting early neurosyphilis can be devised.

Progress and Results: USUHS technician became available September 1977. The CSF of 3 patients (one patient studied twice) were injected into rabbit testis.

Conclusions: It is too early to determine the results of these studies.

Funding Requirements FY-77: \$1,000.00.

Funding Requirements FY-79: \$10,000.00

Publications:

Tramont, E.C. Persistence of Treponema pallidum in Cerebrospinal Fluid. JAMA 236:2206.

Tramont, E.C., The Case Against Benzathine Penicillin as the Treatment of Neurosyphilis. J. Lawton Smith, MD, Editor. Neuro-ophthalmology Update, pp 325-328, 1977.

Tramont, E.C., Chapter 180, Treponema pallidum (syphilis). To be published in Principles & Practice of Infectious Disease, 1978.

Type of Report: Interim.

Work Unit No.: 1904

Title of Project: Access Shunt Infections on Patients Undergoing Kidney Dialysis.

Investigators:

Principal Investigator: Alan Cross, M.D.

Objective: To study the value of access shunt cultures in the diagnosis of infection.

Progress and Results: In 36 patients a comparison of quantitative blood cultures from both the access site and a peripheral vein was used to diagnose access site infection and to monitor the response to therapy. Two patients had a significantly higher bacterial colony count at the access site than from the peripheral culture ("step-up") suggestive of an access site infection. One such patient had prompt removal of the access with control of the infection. The second patient had no decrease in colony counts on access site culture despite vigorous local and systemic antibiotic therapy. His access was removed when progressive infection led to access site hemorrhage. Two patients with gram-negative sepsis had no step-up in bacterial counts indicative of another source of the sepsis and both responded promptly to systemic antibiotic therapy alone with the access left in place. Twelve patients suspected of having access site infection on the basis of pain, redness, edema, fever or pustule formation at the access site had sterile access site cultures. These patients were followed off antibiotics for up to one year and none went on to develop access site infection. Multiple cultures drawn from the access site of a control population of 14 patients undergoing routine hemodialysis were sterile. Quantitative cultures were helpful in both the diagnosis and management of access site infections in patients undergoing chronic hemodialysis.

Conclusions: This technique looks promising but more patients and/or a laboratory animal model is needed.

Funding Requirements, FY-78: \$5,000.00

Funding Requirement FY-79: \$5,000.00

Publications:

Cross, A.S. (abstract) Diagnosis of Access Site Infections in Patients on Hemodialysis. ASM, New Orleans, May 1977.

Type of Report: Interim.

Work Unit No.: 1905

Title of Project: Local Immune Response to Neisseria gonorrhoeae in Humans.

Investigators:

Principal Investigator: Edmund C. Tramont, LTC MC

Objective: To study the local immune response to the mucosal infection caused by Neisseria gonorrhoeae.

Progress and Results: The initial step in the pathogenesis of gonorrhea is likely to be the attachment of gonococci to the surface epithelial cells in the genital tract. Antibodies in genital secretions of patients with gonorrhea have been shown to inhibit attachment of gonococci to epithelial cells.

Gonococcal pili, lipopolysaccharide, and native complex were studied to determine what antigen is primarily responsible for inducing the attachment-inhibiting-antibody.

Gonococcal somatic pili, filamentous protein appendages which extend out from the cell wall have been shown to be important mediators of bacterial attachment to a variety of mammalian cells; while gonococcal lipopolysaccharide has been shown to be an important antigen to which bactericidal antibody is directed. Both of these antigens can be highly purified. Native cell wall complex contains both pili and lipopolysaccharide antigens along with a variety of other, mostly protein, antigens.

Gonococcal pili were purified using the method of Brinton. When the pili preparation was examined using SDS polyacrylamide gel electrophoresis only a single protein band was present as can be seen in the first slide. Ultraviolet spectrophotometry confirmed the absence of contaminating nucleic acid in the preparation.

Lipopolysaccharide was extracted using the phenol-water method of Westphal and further purified using a G-1--Sephadex column.

Native cell wall complex was prepared according to the method of Zollinger. This preparation was shown to contain pili by its ability to inhibit the binding of antigenococcal rabbit antibody to purified pili antigen in the solid phase radioimmunoassay.

The T₂ native cell wall complex used throughout this study was shown to contain lipopolysaccharide by determining the 2 keto-3 deoxy sugar content of the sample using the standard KDO assay. The absence of nucleic acid was confirmed using UV spectrometry. Pili, LPS or NC were used as the antigen in the solid phase radioimmunoassay. Radio-labelled antihuman goat antisera was used as the secondary antibody.

Genital secretions from a single infected patient were collected over a four month period, pooled and concentrated to 25 ug AB/ml. The patient was treated when the diagnosis was first made.

Inhibition of epithelial cell adhesion was determined by incubating the infecting strain of gonococci with the vaginal secretion, then incubating the mixture with buccal epithelial cells at a ratio of 50 organisms to 1 epithelial cell. A smear was made, gram stained, and the number of organisms per epithelial cell were counted. A total of 50 buccal cells were counted per dilution. Controls included epithelial cells incubated without gonococci and with gonococci but without secretion.

Competitive Inhibition of Attachment

Both pili and native cell wall complex were found to competitively inhibit the attachment of gonococci to buccal epithelial cells. The inhibition curve plotted in a dose response mode. Pili purified from a strain of E. coli and native cell wall complex purified from a strain of Pseudomonas aeruginosa were unable to inhibit the attachment of gonococci indicating specificity of the inhibitory action of the gonococcal antigens. Lipopolysaccharide also competitively inhibited the attachment of gonococci. However, lipopolysaccharides purified from strains of Ps. aeruginosa, S. typhimurium and E. coli were all capable of inhibiting the attachment, although not to the same degree as LPS isolated from gonococci. Thus, the inhibitory effects of lipopolysaccharide appears to be a nonspecific reaction.

Because of the competitive inhibition of attachment of gonococci, an inhibition test could not be done and the vaginal secretions had to be absorbed to remove attachment-inhibiting-antibody. The absorptions were carried out by mixing pilus crystals, native complex or, lipopolysaccharide bound to alum, with the vaginal secretion. The antigen complexes were removed by centrifugation. The efficiency of the absorption of gonococcal antibody was determined using the solid phase radioimmunoassay in which the amount of antibody in the absorbed antisera that bound to a specific gonococcal antigen was shown to be reduced when compared to the amount of antigen-binding antibody in unabsorbed sera.

We found that local antibody, inhibiting attachment of gonococci to epithelial cells was removed by the homologous pili and native complex. On the other hand, gonococcal LPS was incapable of removing the inhibiting antibody.

Conclusions:

1. Gonococcal pili and native cell wall complex competitively inhibit the attachment of gonococci to human buccal epithelial cells.
2. Gonococcal lipopolysaccharide inhibits the attachment in a non-specific manner.
3. Gonococcal pili and native complex but not lipopolysaccharide can absorb out the antibodies in vaginal secretions which inhibit the attachment of N. gonorrhoeae to epithelial cells.

Funding Requirement FY-78: \$19,000.00

Funding Requirement FY-79: \$25,000.00

Publications:

Tramont, E.C., Ciak, J. Antigonococcal antibodies in Genital Secretions. 1978 in Immunobiology of Neisseria gonorrhoeae, pp 274-276.

Tramont, E.C. Human Immune Response to Neisseria gonorrhoeae - Prospectives for Vaccine Development. Presented at 32nd Annual Meeting, Soc. Med. Consultants to the Armed Forces. Nov. 1977. (abstract).

Tramont, E.C., Ciak, J., Gilbreath, M., Brinton, C. (abstract) Blockage of Local Antigonococcal Antibody by Gonococcal Antigens. ICCAC, Atlanta, Georgia, 1978.

Tramont, E.C., Hodges, W., Ciak, J. Importance of Antigenic Differences in Gonococcal Reinfection. (Abstract) Clin Res. 1978.

Tramont, E.C., Hodges, W., Ciak, J., Gilbreath, M. Importance of Differences in Attachment Antigens in Gonococcal Reinfection. Submitted for publication.

Type of Report: Interim.

Work Unit No.: 1906

Title of Project: The Limulus Lysate Assay for the Determination of Gram Negative Meningitis Septic Arthritis and Contamination of Intravenous Fluids.

Investigators: Edmund C. Tramont, LTC MC

Objective: To select a reliable and sensitive test to determine the presence of bacterial endotoxin in fluids, especially cerebrospinal fluid, from clinical cases chosen by the Infectious Disease Service.

Technical Approach: Limulus lysates available commercially are being studied. Initially the limulus amoebocyte lysate prepared by Microbiological Associates, Bethesda, Maryland was used. The lysate gel formation reaction occurs in the presence of at least 1.0 ng/ml of endotoxin, according to the manufacturer.

In a comparative study of commercially available lysates in the United States (Applied and Environmental Microbiology 3:1265-1269 (1977)) Wachtel and Tsuji found that other sources than the above had more reliable and more sensitive lysates for gel formation. As a result the lysate from Sigma Chemical Co., St. Louis, Mo. was obtained and tested, since the published report stated that as little as 0.06 ng/ml of E. coli endotoxin could be measured.

Within the last month a quantitative endotoxin analysis has become available from the Millipore Corporation, Bedford, Massachusetts. This is a turbidimetric determination which can be read quantitatively using a spectrophotometer with a precision of 0.005 absorbance units at 360 nm. The manufacturer claims that the assay is sensitive enough to detect as little as 0.005 ng/ml of their reference endotoxin. Basically, the mechanism involved is the combining of endotoxin with limulus amoebocyte lysate proenzyme(s) to form activated enzyme(s) which then unite with particulate protein (coagulogen) to produce aggregated protein that is expressed as turbidity which can be measured. This procedure is currently being used on specimens as they become available.

Progress and Results: Seven specimens were analyzed by the qualitative, i.e. gel formation technique. All failed to produce a positive test, while positive controls were positive.

The quantitative procedure, i.e. turbidimetric technique has been tested on the CSF of four patients. The concentrations of endotoxin present were interpreted as 0.23, 0.12, 0.10 and 0.13 ng/ml respectively. Three "normal" CSF which were tested were found to have 0.07, 0.08, and 0.08 ng/ml respectively. The qualitative, i.e. gel formation procedure tested with two patients were negative.

Conclusions: At the present time the number of patients tested is inadequate to reach any conclusion about the reproducibility or accuracy of the turbidimetric procedure. Further tests will have to be made and the results correlated with the clinical condition of each patient.

It should be noted that all commercial sources of the limulus lysate endotoxin assay procedure stipulate that at the present time their respective tests are not to be used as a substitute for the FDA-approved rabbit test for pyrogens, but only to complement the latter and for research.

Funds Utilized FY-78: \$4,000.00

Funds Requested FY-79: \$9,000.00

Publications: None.

Type of Report: Interim.

Work Unit No.: 1908

Title of Project: Evaluation of Sodium Stibogluconate (Pentostam^R) in the Treatment of Cutaneous Leishmaniasis.

Investigators:

Principal: Jeffrey D. Chulay, M.D., MAJ MC

Associate: Edmund C. Tramont, M.D., LTC MC

Craig J. Canfield, M.D. COL MC

Larry D. Hendricks, PhD, MAJ MSC

Charles L. Pamplin, III, M.D., MAJ MC

Robert E. Desjardins, M.D., MAJ MC

Objectives: (a) To evaluate the clinical efficacy of sodium stibogluconate (Pentostam^R) for the treatment of cutaneous leishmaniasis.

(b) To observe for long term sequelae of cutaneous leishmaniasis and its treatment in military personnel.

Technical Approach: Patients diagnosed as having cutaneous leishmaniasis are offered treatment with sodium stibogluconate (Pentostam^R) either according to the standard treatment plan (manufacturer's recommended therapy for visceral leishmaniasis) or the investigational treatment plan (random assignment to one of three treatment groups: group A, single daily dose; group B, loading dose followed by continuous 24 hour drug infusion; group C, loading dose followed by three equally spaced doses per day). Each course of therapy consists of 10 mg/kd/day (maximum 600 mg/day) for 10 days. Patients are evaluated by clinical appearance of lesions and cultures of lesions. Evidence of toxicity is obtained by monitoring CBC, urinalysis, SMAC-20, and chest x-ray weekly, and EKG daily. For the first five patients in each group of the investigational treatment plan, blood is obtained at intervals for measurement of drug levels to determine the pharmacokinetics of sodium stibogluconate (Pentostam^R).

Patients will be reevaluated by interview, physical examination and culture of lesions three months and one year following treatment. A questionnaire is being developed for follow-up by mail yearly thereafter.

Progress and Results: Seventeen patients have been enrolled in the project during FY-78. The geographic origin of infection for these patients was: Panama, 12; Brazil, 2; Iran, 2; Kenya, 1.

Thirteen patients volunteered for the investigational treatment plan and were randomly assigned to treatment with a single daily dose (4 patients), a continuous 24 hour infusion (4 patients), or three equally spaced doses per day (5 patients). Except for one patient currently receiving his first course of treatment whose response cannot yet be evaluated, all patients in all three groups have had clinical healing of their lesions and negative cultures for leishmania after a single ten day course of therapy.

Four patients elected treatment with the standard treatment plan. One of these, the only patient whose diagnosis could not be confirmed by isolation of leishmania from cultures of skin lesions, was treated on the basis of exposure history and a compatible clinical picture. He was treated with two 10-day courses of 600 mg. sodium stibogluconate (Pentostam^R) daily with no improvement in his skin lesions; the etiology of his disease remains unclear. Two patients were cured, one with a single course and one with three courses of therapy. The remaining patient showed no improvement with the first two courses of therapy and is currently receiving a third course of treatment.

Side effects occurring in the 15 patients who have completed therapy were: no side effects in 10; headache in two; and skin rash, local phlebitis, tinnitus, blurred vision, diarrhea and epigastric discomfort in one each. Abnormal laboratory tests were limited to transient elevation of SGPT in two patients and serum triglycerides in one patient. There were no apparent changes in electrocardiograms.

Eight patients have been seen for follow-up evaluation at least three months after treatment; all were clinically well with healed lesions and negative cultures.

Results of analyses for drug levels are pending.

Conclusion: Sodium stiboglyconate(Pentostam^R) appears to be a safe and efficacious drug for the treatment of cutaneous leishmaniasis. Smaller lesions of recent onset appear to respond more promptly than larger, more chronic lesions.

Funds Utilized FY-78: \$1000.00

Funding Requirements FY-79: \$2000.00

Publications: None.

Type of Report: Interim.

Work Unit No: 1909

Title of Project: Immunological Evaluation of Patients with Cutaneous Leishmaniasis

Investigators:

Principal: Jeffrey D. Chulay, M.D., MAJ MC

Associate: David J. Wyler, M.D.

Edmund C. Tramont, M.D. LTC MC

Objectives: To study antigen-specific and nonspecific humoral and cellular immune responses in patients with cutaneous leishmaniasis.

Technical Approach: Patients with suspected or documented cutaneous leishmaniasis are asked to volunteer to have 50 to 200 ml. of blood obtained by venipuncture for in vitro tests of their immune status. These tests include lymphocyte transformation in response to mitogens and antigens, lymphokine generation, intracellular parasite growth in cultivated monocytes and assessment of "helper" and "suppressor" activity.

Progress and Results: Five patients have been enrolled in the project during FY-78. All patients had lymphocyte transformation responses to leishmanial antigens which were positive, but modest when compared with patients studied previously. Insufficient numbers of patients have been studied thus far to draw conclusions regarding correlations between in vitro immune responses and prognosis.

Conclusions: Leukocytes from patients with cutaneous leishmaniasis respond to leishmanial antigens in vitro.

Funds Utilized FY-78: \$2000.00

Funds Requested FY 79: \$6000.00

Publications: None.

Type of Report: Interim.

Work Unit No.: 2101

Title of Project: Investigation of Vascular Injuries, Vascular Disease, Vascular Grafts and Operating Procedures.

Investigators:

Principal: COL Norman M. Rich, MC

Associate: LTC George J. Collins, Jr., MC, and LTC Paul T. McDonald, MC

Objectives: To establish the best possible diagnosis of vascular injury and disease, to evaluate the methods of management currently used for these problems, and to determine the long term results of current methods of therapy.

Technical Approach: Monthly reports are analyzed and specific topics of interest are investigated in detail. All patients are repeatedly examined on a routine evaluation basis in the Vascular Blood Flow Laboratory.

Progress and Results: The long term follow-up effort continues in the Peripheral Vascular Surgery Clinic and Vascular Blood Flow Laboratory in evaluating patients with vascular disease and those with previous vascular injury who had vascular reconstruction. The fate of various methods of vascular reconstruction remains uncertain and a challenge for the future. Walter Reed Army Medical Center was established in 1950 as the Army's vascular center and we continue in our attempt to document the long term follow-up of these vascular patients. Because the "ideal conduit" has not yet been developed for arterial or venous reconstruction and because we continue to see new and complicated complications in our long term follow-up, this type of registration and follow-up are mandatory. Vascular surgery remains a relatively new field. There has been a particularly dramatic proliferation of new noninvasive diagnostic equipment in the past three years. Medical-engineering advances have been established to enable us to better determine regional blood flow. This has also been appreciated in the civilian community where vascular blood flow laboratories are being developed.

Progress continues similar to that in previous years with our work in the Vietnam Vascular Registry and our long term follow-up of patients in the vascular disease registry. All investigators continue to present numerous papers and publish numerous manuscripts.

Conclusions: The results of this project are reflected by the accomplishment of the investigators and the recognition given to them by their peers and by the vascular societies. This has reflected favorably upon Walter Reed Army Medical Center and the Army Medical Department. This work has allowed the expansion of the twelve year old Peripheral Vascular Fellowship program to now accept two vascular fellows each year. These board certified general surgeons gain additional expertise which will be helpful to them in their senior teaching roles at various Army Medical Centers.

Funds Utilized, FY-78: Approximately \$30,000 of the slightly more than \$31,000 granted by Army R & D Command have been utilized.

Funding Requirements, FY-79: The request is being made for \$30,000. Additional details will be provided as it is submitted to the Research and Development Command of the Office of the Surgeon General. As before, all details will be provided to the Clinical Investigation Service, WRANC.

Publications: An extensive list of publications is available.

Type of Report: Interim

Work Unit No.: 2103

Title of Project: Heparin Dosage During Peripheral Vascular Reconstruction

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: LTC Daniel Kimball, COL Norman M. Rich

Objectives: To determine the safe and effective dosage of heparin for use during peripheral vascular reconstructive procedures.

Technical Approach: Thirty-one patients undergoing peripheral vascular reconstructive procedures were randomly assigned to two groups to receive either 100 or 150 units per kg of body weight of heparin intravenously just prior to cross clamping.

Progress & Results: The study has been completed.

Conclusions: These studies demonstrated that therapeutic heparin levels can be achieved with either dose. Heparin need not be repeated with cross clamp times in the range of one hour. Heparin reversal is mandatory with these doses and is satisfactorily accomplished using .5 mg protamine sulfate per 100 units of initial heparin dose.

Funds Utilized, FY-78: \$500.00

Funding Requirements, FY-79: None.

Publications: A copy of the manuscript which has been accepted for publication in the American Surgeon is attached. This data was also presented at the most recent Southeastern Surgical Congress, and the presentation won the Gold Medal Award as the most outstanding scientific presentation.

Type of Report: Completed.

Work Unit No.: 2104

Title of Project: Evaluation of the Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: MAJ Salvatore Scialla, COL Norman M. Rich,
MAJ Earl Ferguson, MAJ Patrick Clagett,
LTC Paul T. McDonald, and Mr. Charles Barr

Objectives:

- 1) To determine the relative effectiveness of several platelet active drugs in suppressing in vivo and in vitro platelet function.
- 2) To determine whether or not these drugs cause a lowering of coagulation factors.
- 3) To determine ^{if} suppression of platelet function in patients with intermittent claudication results ~~and~~ objective improvement in exercise tolerance.

Technical Approach: Patients ranging in age between 40 and 70 years of either sex with intermittent claudication documented by lowering of ankle pressure after exercise have been randomized into four treatment groups. One treatment group receives placebo, one treatment group receives 600 mg per day of aspirin, one treatment group receives 600 mg per day of aspirin and 100 mg per day of persantin, and one treatment group receives 200 mg of sulfinpyrazone four times daily. Patients have a full coagulation screening battery including prothrombin time, activated partial thromboplastin time, fibrinogen, factors II, V, VII-X, VIII antigen, IX, X, XI, XII, antithrombin III, fibrin split products, and protamine sulfate ~~para-~~ coagulation. The tests are done before taking medications, after being on medications for two weeks, after being on medications for two months, and after being on medications for six months. In addition to this, patients have arm and ankle pressures before and after treadmill exercise at the same time intervals.

Progress & Results: This study is going along quite well at this point. Eighty-two patients have been entered into this study, and this is over one half of our anticipated number. So far there have been very few patients who have had to drop out of the trial period. One patient developed a rash while taking drugs and was withdrawn from the trial period. Another patient was withdrawn from the trial because of inability to keep the appointments.

Conclusions: The study continues and no conclusions can be drawn at this time.

Funds Utilized, FY-78: \$3,829.00

Funding Requirements, FY-79:

Supplies: \$3,000.00
Travel: \$300.00
Other: Publication cost, \$200.00

Publications: None.

Type of Report: Interim

Work Unit No.: 2105

Title of Project: Rapid Screening for Coagulation Abnormalities

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: LTC Daniel Kimball, COL Norman M. Rich,
MAJ Salvatore Scialla, and Mr. Charles Barr

Objectives: To develop techniques whereby sizable numbers of patients can be screened for hypercoagulability. The objective of the study is to be able to screen as many as twenty patients per day.

Technical Approach: Fifty patients from the Peripheral Vascular Surgery and Hematology-Oncology Clinics with suspicion of hypercoagulability will have coagulation screening batteries and thromboelastography performed. In addition, twenty healthy volunteers will be examined. After the determinations are made, the results of thromboelastography will be compared to the results of the screening battery. If the results of thromboelastography agree with the results of broad screening with coagulation test, thromboelastography will then become the principle mode of screening.

Progress & Results: A direct writing thromboelastograph has been ordered. This equipment has not been previously available at this Center. For this reason, no patients have actually been entered into the study.

Conclusions: Not applicable.

Funds Utilized, FY-78: None.

Funding Requirements, FY-79:

Equipment:	Thromboelastograph, \$6,800
Supplies:	\$1,000
Travel:	\$300.00
Other:	Publication costs, \$200.00

Publications: Not applicable.

Type of Report: Annual, Interim.

DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-SN

SUBJECT

Annual Progress Report, Clinical Investigation Program, Work Unit #2205, Clinical Data Acquisition Project, A Grant Application


TO
C, Clin Inv Svc

FROM
Sanford Wright, MAJ, MC
Asst C, Neurosurgery Service

DATE
22 Sept 1978

CMT 1

The Dean of the Uniformed Services University of the Health Sciences felt that this computer aided clinical investigation project is not capable of being supported by the current or projected research budget. Therefore, because of the lack of funds this entire project was not finalized or approved. For these reasons a progress report is obviously not necessary.


SANFORD WRIGHT, M.D.

MAJ, MC

Asst C, Neurosurgery Service

Work Unit No.: 2304

Title of Project: Technician-Assisted and Computer-Assisted
Ophthalmological Care.

Investigators:

Principal: COL Budd Appleton

Associate: LTC Kenyon K. Kramer

Objectives: (1) To evaluate current methods of refractometry in terms of which type and methods appear to have the greatest military medical application.

(2) To evaluate the potential of civilian-trained Ophthalmic Medical Assistants (Technicians) for integration as members of the Army Eye-Care Team.

(3) To evaluate methods of training Ophthalmology residents so as to include maximum utilization of allied health personnel in their training for clinical practice.

(4) To determine the optimum composition of a Program of Instruction (POI) for Ophthalmic Medical Assistants trained to work in AMEDD MTF's.

Technical Approach: (1) Comparison studies of time required to do manual refractometry (retinoscopy versus the time required to use clinically available automated retinoscopes (Auto-refractor 6600, Ophthalmetron and Dioptron).

(2) Measurement of increase in rate of patient throughput per ophthalmologist by using a civilian-trained Ophthalmic Technician to perform selected psychomotor tasks ordinarily performed by the doctor. Measurements to be made using several samples of ophthalmologists and several samples of technician, plus whatever variations in task arrays and order appear to be appropriate. Measurements to be obtained using two or more Ophthalmic Technicians working simultaneously with the same ophthalmologist if this is feasible.

(3) Establishment of proposed SOP's for:

a. Use of one or more Ophthalmic Technicians by an ophthalmologist in an AMEDD MTF Eye Clinic.

b. A Program of Instruction for Army-Trained Ophthalmic Medical Assistants trained specifically to do work in AMEDD MTF's.

c. Integration of training in utilization of Ophthalmic Medical Assistants into the POI's for Ophthalmology residents trained in AMEDD MTF's.

Progress and Results: Project has been under way twenty-one (21) months, of which approximately two (2) months were required for task partition and familiarization with clinical procedures. The remaining time has been devoted to Objective 2. and Objective 3., and their technical approaches. The performance levels of six Ophthalmology residents have been evaluated as of this date. Their increases over base-line performance have ranged from approximately 50% to approximately 300%, using an Ophthalmic Technician in the format originally devised by the Investigators. Additional preliminary efforts have been made to evaluate a different (triage) format utilizing an Ophthalmic Technician, but thus far no attempt has been made to produce data utilizing this system comparatively.

Conclusions: Ophthalmic technicians using automated testing devices provide a cost effective means of increasing the quantity of quality ophthalmic care. Minimum work space requirements are two examining areas per ophthalmologist.

Type of Report: Terminated

Work Unit No.: 2306

Title of Project: Clinical Quantification of Intraocular
Malignant Melanoma Volume

Investigators:

Principal: Kenyon K. Kramer, LTC, MC, USA

Objectives: To develop a technique to quantitate the size of intraocular malignant melanomas in vivo, since this is an important prognostic parameter and may become an important management parameter.

Approach: B Scan water-bath ultrasonography after the method of Jackson Coleman, M.D., will be used to measure the malignant melanomas in vivo in order to determine three representative dimensions. Additionally the Bronson Turner ultrasound unit will also be used to make the same measurements when possible.

Progress & Results: Six additional lesions have been measured in vivo and have come to histopathology with the following combined results:

3rd Report:

	Single Largest Dimension	% Error
	<u>Coleman</u>	<u>Bronson-Turner</u>
8	-20	+18
9	+3	-3
10	-8	--
11	+33	+67
12	-27	-27
13	--	+13

Mean Algebraic Error = 3.8

Mean Algebraic Error = +13.6

Mean absolute % error 1 thru 7 = 32.5

Mean absolute % error 8 thru 13 = 18

Conclusions: As can be seen by the above figures a small improvement has been made in the percentage of errors and perhaps minimal further improvement can also be made by further refinement of certain constants.

However, after measuring some 13 melanomas I believe we may be near the limit of the apparatus which is currently available.

Funds Utilized FY 78: 0

Funding Requirements: FY 79: 0

Publications: None

Type of Report: Interim

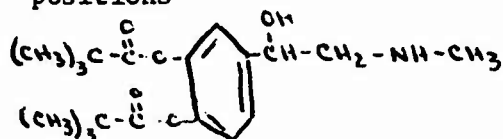
Work Unit No.: 2307

Title of Project: Evaluation of Dipivalyl Epinephrine in the Treatment of Glaucoma

Investigators: Lee Jampol, M.D. (former MAJ, MC, USA)
William Rimm, MAJ, MC, USA

Objectives: To evaluate Dipivalyl Epinephrine and its efficacy in the treatment of chronic open angle glaucoma.

Technical Approach: Dipivalyl Epinephrine (DPE) is an analogue of epinephrine that differs from the parent compound by the addition of 2 pivalic acid groups at the meta - and para - positions



By virtue of these pivalic acid groups, DPE should be more lipophilic than epinephrine and should, consequently, penetrate the cornea more readily. Further, degradation by catechol o-methyl transferase (COMT), the main metabolic pathway, must await removal of the pivalic acid group at the meta-position by some local esterase before it can act. [MAO pathway is not affected.] Thus DPE should have a prolonged effect.

Previous studies suggest that DPE significantly lowers intraocular pressure (IOP) in concentrations as low as 0.025%, produces mydriasis in concentrations of 0.1% and greater, and has significantly fewer adverse reactions in those patients with intolerance to topically applied epinephrine preparations.

We studied the effect of DPE in the control of open angle glaucoma in 17 patients (10 males and 7 females) with a median age of 61.2 years (range 47 to 74) during a treatment period of up to 1 year.

Patients were selected on the basis of:

- 1) age greater than 18 years;
- 2) open angle glaucoma as defined by characteristic field loss in at least one eye and IOP greater or equal to 25mm Hg in both eyes; or normal fields with IOP greater or equal to 30mm Hg in both eyes;
- 3) IOP measured off epinephrine treatment but concomitant therapy with non-epinephrine drugs allowed if the same in both eyes and continued throughout the study;
- 4) no aphakic patients;
- 5) no patients with Grade 0 to 2 angles (Becker & Schaeffer); and
- 6) no patients with a history of cardiac disease.

The study was designed such that:

- 1) all patients underwent a minimum 2 weeks washout period with removal of all epinephrine medications prior to initiation of treatment with DPE;
- 2) concomitant medications were discontinued or decreased to qualify the patient for entry into the study;
- 3) patients fulfilling the selection requirements as determined by control examinations on Day - 7 and Day 0 were started on 0.1% DPE, 1 drop in both eyes at 9 AM and 9 PM, and were continued on any concomitant medications;
- 4) follow up examinations were conducted on Day 14 and months 1 through 12. Examinations consisted of visual acuity, pupil size and response, slit lamp examination, intraocular pressures and ophthalmoscopic examination. Additionally, on Day 0 and months 6 and 12, all patients also had visual fields, gonioscopy, measurement of cup-disc ratios, hematologic and blood chemistry evaluations, and cardio-vascular evaluations;
- 5) patients were maintained on 0.1% DPE as long as safe IOPs were maintained without toxicity to the medication or progressive visual field loss; and
- 6) if uncontrolled on 0.1% DPE, the patient was switched to 0.25% DPE. If still not controlled, the patient was moved to 2% epinephrine HCl to verify the patient was, in fact, an epinephrine responder. Responders were moved back to 0.25% DPE to ascertain they were true treatment failures. Non-responders were discontinued.

Progress and Results: A total of 17 patients were entered into the study of which 9 completed the study. Six patients were eliminated from the study due to inadequate control of IOP and all 6 were found to be epinephrine non-responders. Two patients were eliminated from the study due to allergic reactions. One of these had a follicular conjunctivitis and the other, with minimal objective findings, was discontinued at his request due to subjective intolerance to the drug.

The mean rise in IOP during the initial week of the washout period for those patients previously on epinephrine was 12% but the reliability of this figure is suspect due to the uncontrolled nature of this part of the protocol and the number of patients.

There was no significant effect on the visual acuity, CBC, SMAC 20, Blood Pressure or Pulse rate by the DPE.

The mydriatic effect of 0.1% DPE was found to increase the mean pupil size 10% but 9 of the 17 patients were on concomitant miotic therapy. For those patients on no concomitant miotic therapy the increase in mean pupil size was 16.6%

The effect of DPE on IOP is shown in Table I. As is shown, there is an initial good lowering of IOP with subsequent rise in the first to second month.

When we eliminate those patients who were subsequently found to be epinephrine non-responders (Table II) we see that the pressure lowering effect of DPE is fairly uniform throughout the study - in the range of 25%.

Table III shows the incidence of adverse reactions to DPE. Although there appears to be a significant incidence of subjective complaints, all patients who had been on other epinephrine preparations prior to the study claimed that DPE was at least as comfortable and most claimed significantly fewer side effects. Two patients were discontinued due to side effects. One due to severe burning and stinging, although there was no objective evidence, which he claimed was just as bad as with epinephrine. The second patient was discontinued due to an allergic follicular conjunctivitis with her concurrent complaint of tearing. It is interesting to note that she had no previous problems with epinephrine.

Conclusions: Topically applied epinephrine compounds are widely employed in the management of glaucoma. The decrease in IOP that occurs is a result of the drugs adrenergic effect on the ciliary body and outflow pathways but many patients must discontinue these drugs because of the development of systemic and local effects. In approaching the problem of epinephrine sensitivity, many of the side effects can be reduced by decreasing the concentration or switching to a different formulation.

Alternatively, a drug that penetrates the cornea more readily and can be used in minimal concentrations while effectively lowering IOP would avoid many of the extraocular problems. This study supports the finding that DPE is effective in lowering the IOP in epinephrine responders and is subjectively as comfortable; if not more so, than commonly used epinephrine preparations. This is not to say that DPE is better than epinephrine. It's primary advantage at this point in time is that it appears to be better tolerated by those individuals with epinephrine sensitivity. Its pressure lowering properties appear to be on a par with current preparations of epinephrine. DPE should be looked on as an alternative and not a replacement drug for currently available preparations of topically applied epinephrine.

Fundus Utilized FY-78: None

Funding Requested FY-79: None

Publications, FY-78: None - Paper presented at the BiAnnual WRAMC Ophthalmology Alumni Meeting, April 1978

Type of Report: Completed (The original plan to incorporate 25 patients into the protocol was not feasible due to the prolonged recovery from an injury by one of the investigators.)

TABLE I

MEAN IOP CHANGES WITH DPE

	n	\bar{X} IOP OD	\bar{X} IOP OS	\bar{X} IOP OU	% Fall OU
Day 0	17	27.3	27.6	27.4	-----
Day 14	17	21.0	20.8	20.9	23.4
Month 1	16	23.1	22.9	23.0	16.0
Month 1.5	4	30.2	30.5	30.4	- 10.6
Month 2	13	19.9	22.7	21.3	22.6
Month 2.5	3	23.2	26.0	24.6	10.2
Month 3	12	21.1	20.2	20.6	24.8
Month 4	11	21.5	20.7	21.1	23.4
Month 5	10	10.7	19.5	19.6	28.5
Month 6	11	21.3	21.3	21.3	22.6
Month 7	10	19.6	19.9	19.8	27.7
Month 8	10	18.6	19.4	19.0	30.7
Month 9	10	17.9	18.1	18.0	34.3
Month 10	10	18.6	18.9	18.8	31.4
Month 11	9	18.2	18.7	18.4	32.8
Month 12	9	20.0	20.3	20.2	26.3

TABLE II

MEAN IOP CHANGES WITH DPE FOR EPINEPHRINE RESPONDERS ONLY

		<u>n</u>	<u>\bar{X} IOP</u>		<u>\bar{X} IOP</u>	<u>% Fall</u>
			<u>OD</u>	<u>OS</u>	<u>OU</u>	<u>OU</u>
Day	0	11	25.9	27.3	26.6	----
Day	14	11	19.5	19.7	19.6	26.3
Month	1	10	21.0	21.1	21.0	21.1
Month	2	10	20.8	12.4	21.1	20.7
Month	3	10	20.6	20.4	20.5	22.9
Month	4	10	21.4	20.9	21.2	20.3
Month	5	9	19.7	19.4	19.6	26.3
Month	6	10	20.4	20.9	20.7	22.2
Month	7	10	19.6	19.9	19.8	25.6
Month	8	10	18.6	19.4	19.0	28.6
Month	9	10	17.9	18.1	18.0	32.3
Month	10	10	18.6	18.9	18.8	29.3
Month	11	9	18.2	18.7	18.4	30.8
Month	12	9	19.6	20.3	20.0	24.8

TABLE III

<u>SIDE EFFECTS</u>	<u>0.1% DPE</u>	<u>0.25% DPE</u>
Subjective:		
Blurring	12 (8.8%)	2 (8%)
Burning/Stinging	3 (2.2%)	1 (4%)
Tearing	3 (2.2%)	1 (4%)
Redness	2 (1.5%)	2 (8%)
Light Sensitivity	1 (0.7%)	-----
Objective:		
Trace Injection	21 (15.3%)	13 (52%)
1+ Injection	11 (8.0%)	3 (12%)
2+ Injection	-----	3 (12%)
3+ Injection	-----	1 (4%)
Follicular Conj.	4 (2.9%)	-----
1+ Lid Erythema	1 (0.7%)	-----
Total Patient Visits	181	25

Work Unit No.: 2308

Title of Project: Scleral Buckling for Retinal Detachment 1973-1976.
A Retrospective View.

Investigators:

Principals: Glenn N. Pomerance, CPT MC
Resident in Ophthalmology

Paul V. Whitmore, LTC MC
Assistant Chief, Ophthalmology Service

Objectives: The purpose of this clinical review, therefore, is to present our experience in scleral buckling and to draw some conclusions from our experience.

Technical Approach: Attempts will be made to create a listing of all cases, to include demographic information, diagnosis, indications for surgery, hard preoperative data (fundus drawings, etc), surgical procedures performed (to include type of element utilized, method of placement, drainage versus nondrainage), complications of surgery and postoperative results with specific interest on resultant visual acuity as compared to degree of detachment preoperatively.

Attempts will also be made to obtain follow-up data on as many patients as possible. This will be accomplished by contacting the patients themselves, their referring physicians, or both.

Arrangements will be made for as many patients as possible to undergo a follow-up exam at WRAMC. If this is not feasible, the patient will be requested to visit the nearest Army Medical facility for a follow-up examination by an Ophthalmologist. A questionnaire will be devised to provide the examiner with guidelines so that base-line data for the study will be obtained.

Conclusions: This project is proceeding with data collection on all cases in study (approximately 150) from inpatient records. It is anticipated that this will be completed by 15 June 1979.

Second stage of protocol, examination of patients, and collection of follow-up data will be continued by principal investigator (Dr. Whitmore) and another resident to be named.

Type of Report: Interim

Work Unit No.: 2309

Title of Project: A Study of Eye Trauma and Treatment in the Military

Investigators: Principal - Howard P. Cupples, CPT, MC, USN
Associate - Paul V. Whitmore, LTC, MC, USA

Objectives:

1. To determine the role of vitreous surgery in the management of ocular trauma.
2. To compare the results of ocular trauma cases managed by vitreous surgery with the results of ocular trauma cases managed in the past by conventional methods.
3. To use animal studies in order to refine vitreous surgery techniques and to develop new approaches to problems in the management of ocular trauma.
4. To develop plans for the efficient management of ocular combat injuries based upon the analysis of data collected during the study.

Progress and Results:

Sixteen (16) cases of ocular trauma have been managed at Walter Reed Army Medical Center using vitreous surgery techniques. A combined series of fifty (50) cases between the National Naval Medical Center and Walter Reed Army Medical Center was reported at the 1978 Biennial Walter Reed Army Medical Center Ophthalmology Postgraduate meeting. In this report a classification of types of injuries was developed which is expected to facilitate the determination of optimal time for intervention with vitreous surgery in various types of injuries.

Based on our early experiences with removal of large non-magnetic intraocular foreign bodies, a technique has been developed which employs vitreous surgery and permits removal of the foreign body through the anterior chamber of the eye without causing additional damage to the posterior segment of the eye. This technique has been reported by us at the 1978 meeting of the Wilmer Residents Association of Johns Hopkins University Hospital.

Funds Utilized FY 78: None

Funding Requirements FY 79: None

Work Unit No. 2309 (continued)

Publications:

Cupples H, Whitmore P, Parver L. Pars Plana Vitrectomy: An Advance in Management of Severe Ocular Trauma. US Navy Medicine 68:26-29, 1977.

Type of Report: Interim

Work Unit Number: 2310

Title of Project: Intraocular Lenses

Investigators:

Principal: Kenyon K. Kramer, LTC

Associate: Floyd L. Wergeland, COL

Norman N.K. Katz, LTC

Objectives: To evaluate intraocular lenses in the treatment of aphakia.

Technical Approach: Intraocular lenses will be implanted in selected patients either at the time of cataract extraction, or at a second operation following the extraction. This is part of a nationwide collaborative study to determine the incidence of adverse defects.

Progress & Results: Two patients have had intraocular lenses implanted at the beginning of this study without adverse affects.

Conclusions: No conclusions are possible at this early date.

Funds Utilized, FY-78: None

Funding Requirements, FY-79: None

Publications: None

Type of Report: Interim

Work Unit No.: 2508 (formerly #201)

Title of Project: An Experimental Analysis of Aural Rehabilitation Using Programmed Instruction

Investigators:

Principal: Edward B. Muth, M.A.
Aural Rehabilitation Section, AA&SC

Associate: Charlene K. Scherr, M.A.
Aural Rehabilitation Section, AA&SC

Objective: To provide three programmed presentations for orientation to effective hearing aid use

Technical Approach: Use of tape recorded 3-voice narration film slide presentations in three (3) sound slide projectors. Presentations are to be 20 minutes duration, 80 slides each. Separate presentations will allow separate individual or smaller group presentations geared to the differentiated needs of different patients. This will permit study and analysis of different rates of progress in rehabilitation, if any.

Progress and Results: Original color film series was lost and had to be retaken. First set of 80 slides produced were put into immediate use. These slides have been sent for photo reproductions. Due to environmental limitations, additional presentation booths could not be created in old quarters, but can be implemented in the New Treatment Facility after moving there.

Conclusions: A study has shown that persons issued hearing aids that completed the programmed instruction were able to grasp the essential requirements for successful use and communication with only a minimum of time spent at the center--the so-called "Quickly" delivery. This has proven to be a popular course taken by the more busy 'executive' type individual and the indisposed who have reasons not to undergo the two week course.

Funds Utilized, FY 78: None

Funding Requested, FY 79: None

Publications, FY 78: None

Type of Report: Termination

WORK UNIT NUMBER: 2510

TITLE: A Multidimensional Assessment of Stuttering Severity

INVESTIGATORS:

Principal: Robert A. Prosek, Ph.D.
Associate: Brian E. Walden, Ph.D.
Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVE: To determine the parameters of stuttered speech that are used by speech-language pathologists to rate the severity of stuttering.

TECHNICAL APPROACH: Fifteen male stutterers, selected from the patients seen at the Army Audiology and Speech Center, WRAMC, provided the speech material used in the study. It was determined that two of these patients did not exhibit sufficient stuttering behavior to be included in the experiment. The remaining 13 stutterers were between the ages of 19 and 45 years (mean age, 24 years). Audio tape recordings were made as each stutterer read the Amplifier Passage (Fairbanks, 1960) in a sound-treated room at a constant mouth-to-microphone distance of one meter. The stutterers were instructed to use their normal rate, loudness and pitch and to make no special attempt to control their stuttering behavior.

The individual differences model of multidimensional scaling used in this study required each stimulus to be paired with every other stimulus in the ensemble for presentation to the judges. Since it would have been impractical to pair the entire Amplifier Passage across the 13 stutterers, the procedures outlined below were followed to select one sentence for each stutterer which would be used for the judgment task.

Measurements of disfluency were made for each sentence of the passage for each stutterer using the classification scheme outlined by Johnson, Darley and Spriestersbach (1963). The classifications included were moments of stuttering, interjections, part-word repetitions, word repetitions, phrase repetitions, revisions, incomplete phrases, broken words, prolonged sounds and reading rate in words per minute. In addition, the number and duration of intrasentence pauses were measured by analyzing each sentence with the histogram shaper of a computer of average transients (CAT) in a manner similar to that described by Love and Jeffress (1971). The output of the CAT was a frequency distribution of intrasentence pauses obtained with a time resolution of ± 10 msec. Based upon the findings of Love and Jeffress (1971), only pauses of 100 msec or longer were included in the measurements. Finally the duration of each prolongation was measured from sound spectrograms with an accuracy of ± 10 msec. The measurements described above were made by the principal investigator whose reliability across the 13 measures was 0.96.

In order to select the sentence for each stutterer to be used in the judgment task, the measurements for each sentence of the passage

were converted to Z-scores and summed across the variables. For a given stutterer, the sentence yielding the highest summed Z-score was used in the study. This procedure insured that the sentence selected for each stutterer maximized stuttering behavior. A stimulus tape was prepared by pairing each stutterer's sentence once with the sentence of each of the other 12 stutterers. Only one sentence order was used since pilot data indicated that sentence order did not significantly influence listener judgments. The stimulus tape, therefore, consisted of 78 sentence pairs, with the order of the pairs determined from a table of random numbers.

Eight speech-language pathologists served as judges for the experiment. The sentence pairs were presented via a loudspeaker in a sufficiently quiet test room (ambient noise level, 48 dB(C)). The loudness of the recordings was adjusted to a comfortable listening level. The judges were instructed to indicate which member of each pair was the more severe stutterer, and then to indicate the confidence with which this judgment was made. Confidence was rated on a five-point scale where "one" represented a high degree of confidence, and "five" represented no confidence. This procedure assumed that a confidence rating of "one" indicated that the two stutterers were perceived as very dissimilar in stuttering severity. Conversely, when a judge rated his confidence as "five", the two stutterers were very similar in stuttering severity.

The judgment task was repeated on four occasions over a three-week period. The first two sessions were regarded as practice, and these data were not used in the analysis. The confidence ratings of the third and fourth sessions had a mean product-moment correlation of 0.77 across the eight judges, and these ratings were pooled for each judge and arranged in a lower triangular matrix.

PROGRESS AND RESULTS: The eight matrices were analyzed via the computer program INDSCAL which is based on the individual differences model of multidimensional scaling. Multidimensional scaling procedures have the advantage of using the psychological data alone to determine the perceptual dimensions used in making the judgments. That is, the analyses make no a priori assumptions concerning the number or the nature of any relevant physical variables which may underlie the psychological judgments of the subjects. The individual differences model offers a further advantage in that it also provides weights indicating the degree to which each judge relied on the various perceptual dimensions.

The matrices were analyzed in seven through two dimensions. The two dimensional solution, which explained 50% of the variance, is discussed here since it provided dimensions which were readily interpretable. In Figure 1, the stutterers are displayed in the two dimensional perceptual space provided by the INDSCAL analysis. Each number in the figure represents one of the 13 stutterers. In order to aid interpretation, the two dimensions were correlated with the measurements of stuttering behavior described previously. A product-moment correlation of -0.80 was found between the first dimension and reading rate, and a

coefficient of 0.75 was found between the second dimension and the number of pauses within a sentence. In terms of the figure, stutterers who are to the right of the origin had slower reading rates than stutterers who are to the left of the origin. Further, stutterers lying below the origin had fewer pauses within a sentence than stutterers who are above the origin. The correlation between the first and second dimensions was 0.51 whereas that between reading rate and number of pauses was -0.50. These moderate correlations were expected and indicate that, as reading rate increases, it is likely that the number of intra-sentence pauses will decrease.

As mentioned earlier, the individual differences model underlying INDSCAL provides a useful method for comparing judges. The analysis provides a set of weights which characterize the extent to which a judge relied on each of the two dimensions in making his severity judgments. These weights are conveniently displayed in Figure 2. The coordinates of the figure are the two psychological dimensions, and the data points are the judges. In general, the farther from the origin that a judge lies along a dimension, the greater the weight given to that dimension by the judge. Further, the closer a judge is positioned to the main diagonal, the more equally he weighted the two dimensions. It is apparent that the judges can be divided roughly into three groups based upon the relative weight given to each of the dimensions. Although there are many measurable parameters of stuttering behavior present in the speech samples, most judges appear to use a single parameter in judging stuttering severity. This interpretation of the data assumes that the higher dimensions, which could not be labeled using the available physical measurements, were not influencing the judges to any great extent. In this regard, it should be noted that there is a relationship between the number of stimuli included in a multidimensional scaling analysis and the number of meaningful dimensions which can be recovered from the analysis (Sherman, 1972). It is possible that, had more stutterers been included in the sample, more interpretable dimensions would have emerged.

CONCLUSIONS: Because of the small number of judges and stutterers used in the study, the results cannot be safely generalized to the broad populations of all stutterers and speech-language pathologists. Assuming that the judges and stutterers used are representative, however, the results do have important implications for clinicians and researchers.

Since most of the judges appeared to rely on a single dimensions in making severity judgments, and since the dimension was not the same for all judges, some pretraining may be necessary to insure that judges are responding to the same attributes of stuttered speech or to those attributes of interest to a particular investigator. Since severity of stuttering apparently means different things to different people, the results indicate that more studies of the perceptual properties of stuttering severity need to be conducted to determine the dimensions that are important to various groups of speech-language pathologists.

That reading rate should emerge as a correlate of the first dimension is not surprising since rate has been advocated as a useful

index of disfluency (Sander, 1961; Minifie and Cooker, 1964). In addition, Young (1961) found that rate was one of three variables that could be used to predict stuttering severity judgments, and Prins and Lohr (1972), in a factor analysis of stuttering behavior, found that rate contributed to their first factor. What is surprising is that none of the more commonly used measures of stuttering, such as frequency of stuttering or frequency of part-word repetitions, emerged as a correlate of the perceptual dimensions. This does not mean necessarily that these more traditional measures are unrelated to stuttering severity totally, but the data argue that, at the very least, the relationship is not a simple one.

The second interpretable dimension, pauses, is an often neglected parameter of stuttered speech in general. Love and Jeffress (1971), in a study of the fluent speech of stutterers, found a significantly greater number of pauses of 125 msec or longer in the speech of stutterers than that of nonstutterers. The results of the present study extend the findings of Love and Jeffress in that the number of pauses also is perceptually important, at least for some judges, when assessing stuttering severity.

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FUNDS UTILIZED, FY-78: NONE

FUNDING REQUIREMENTS, FY-79: NONE

PUBLICATIONS: The inclosed manuscript entitled "A Multidimensional Analysis of Stuttering Severity" has been submitted for publication to the Journal of Speech and Hearing Disorders.

TYPE OF REPORT: COMPLETED

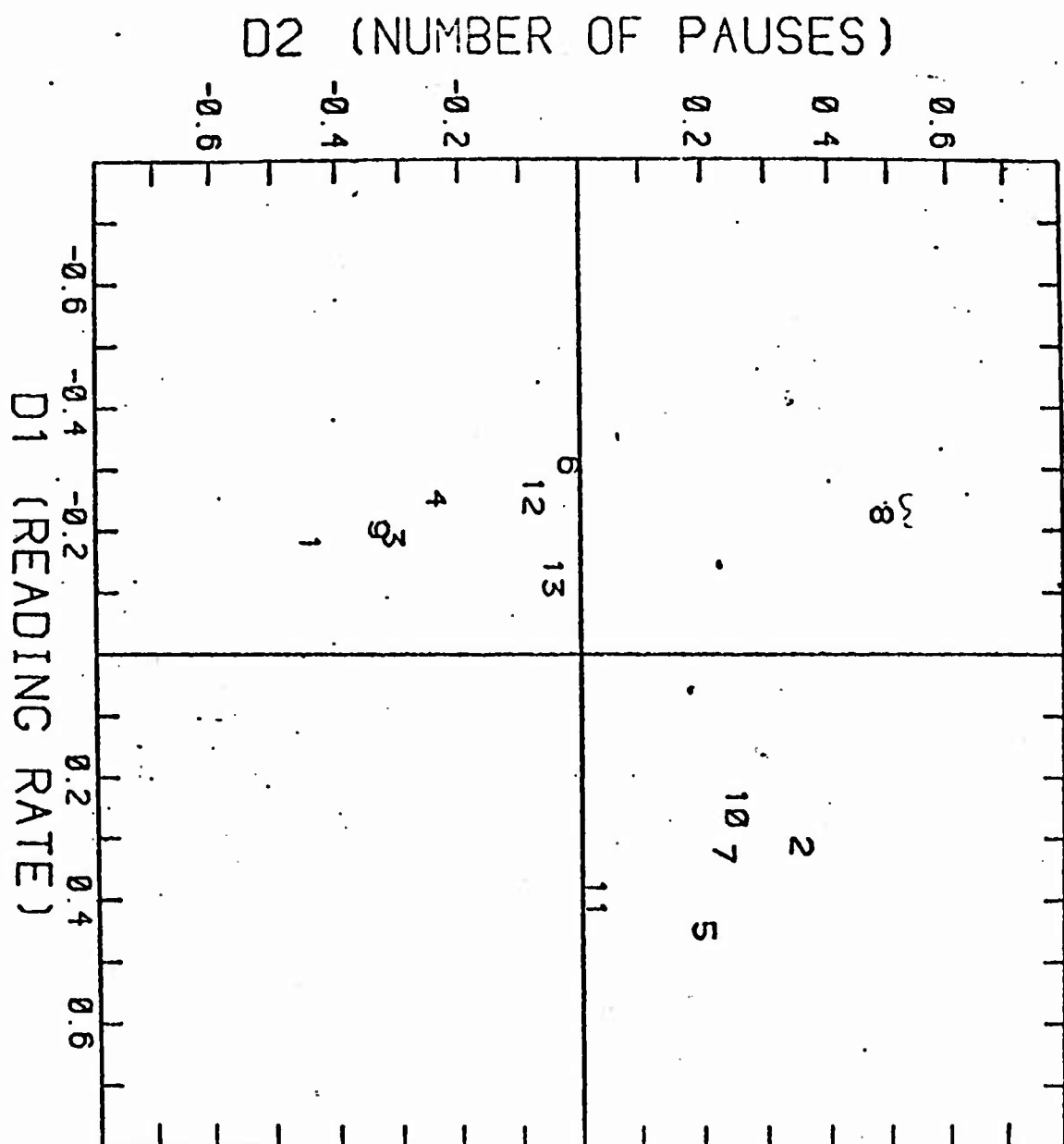


Figure 1. Two dimensional perceptual space in which each number represents one of thirteen stutters.

D2 (NUMBER OF PAUSES)

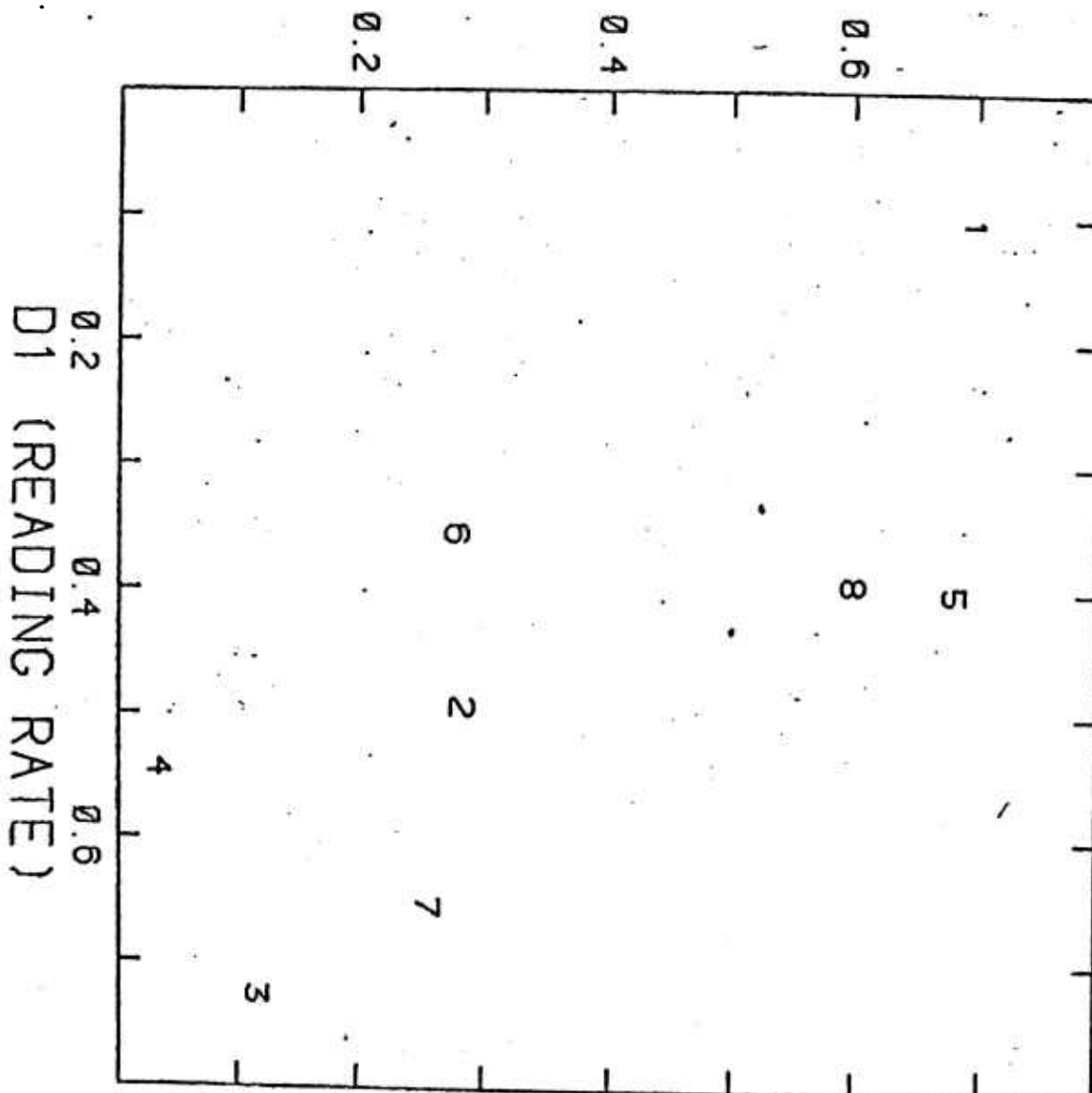


Figure 2. Two-dimensional perceptual space in which each number represents one of eight speech-language pathologists.

WORK UNIT NUMBER: 2512

TITLE: Effects of Hearing Impairment and Acoustic Filtering on the Perception of Speech

INVESTIGATORS: Principal: Brian E. Walden, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

OBJECTIVE: The objective of this experiment is to describe those effects of hearing loss on speech perception which cannot be accounted for on the basis of the frequency distortion imposed by reduced auditory sensitivity. Specifically, the purpose is to determine which speech sounds (or classes of sounds) are perceived similarly and differently through an impaired ear and a normal ear listening through a filter network which has been matched to the impaired ear's audiometric configuration.

TECHNICAL APPROACH: Consonant confusion matrices have been obtained for 13 adults with unilateral hearing impairments. The consonants were presented without any external distortion to the impaired ear. For the normal ear, however, the stimuli were presented through a multi-filter network which was adjusted to match the configuration of the hearing loss in the impaired ear. In-addition, pairs of consonants were presented sequentially to the two ears for judgment of consonant similarity using an equal appearing interval scale. The resulting data were analyzed to reveal which consonants (and classes of consonants) are perceived differently through the impaired ear and the filter network. As a check on the validity of the supra-threshold audiogram matching procedure, consonant confusion matrices have been obtained for 6 normal-hearing adults. Frequency distortion of varying amounts were introduced into the audio circuit to one ear via two passive band-pass filters. The multi-filter was then used to match the frequency distortion in the opposite ear using the audiogram matching procedure. Frequency responses of the two filter networks were obtained in order to compare them for similarity, and consonant confusion matrices were obtained for both ears.

PROGRESS AND RESULTS: It is anticipated that data will be obtained for 10 normally-hearing subjects and 10 unilaterally impaired subjects. Data for 5 of the 13 unilaterally impaired subjects that have been run to date had to be discarded because the nature of their hearing impairments (i.e., flat audiometric configurations) resulted in very few confusions in the normally-hearing ear when listening through the multi-filter. As a result, standard analyses could not be applied to these matrix data. Data for 6 of the 10 normally-hearing subjects have been obtained to date. The confusion matrix data for the normally-hearing subjects and the hearing-impaired subjects have been analyzed via INDSCAL and KYST multi-dimensional scaling programs to derive the underlying perceptual features. The features derived from the

multi-dimensional scaling analysis were then used as criterion dimensions for a SINFA analysis of the confusion matrices for each subject. Since all ears were treated separately, the resulting data consisted of a SINFA analysis of 28 confusion matrices - 16 for the 8 hearing-impaired subjects and 12 for the 6 normally-hearing subjects. Cross products between the feature weights for each ear and every other ear have been computed. Currently these data, as well as additional recognition data, are being analyzed to determine which consonants and features are perceived differently through the impaired ear and the normal ear listening through the multi-filter.

CONCLUSIONS: The preliminary analysis of the data suggests that there is a substantial amount of distortion in the impaired ear which is not accounted for by the multi-filter. Specifically, recognition performance in the impaired ear is substantially below that of recognition in the normal ear listening through the multi-filter. Correlations between the phoneme recognition scores for the two ears of the hearing-impaired subjects are moderate-to-low. There is some preliminary evidence, however, to suggest that the pattern of feature recognition may be similar between the two ears of the hearing-impaired subjects despite the differences in recognition scores. The data of the normal-hearing subjects suggests that the audiogram matching procedure is quite efficient in matching the frequency distortion of one ear on the multi-filter.

FUNDS UTILIZED, FY-78: None

FUNDS REQUESTED, FY-79: None

PUBLICATIONS: The results to date of this experiment are being presented at the joint meetings of the Acoustical Society of America and the Acoustical Society of Japan, meeting in Honolulu in November 1978.

TYPE OF REPORT: Interim

Work Unit No.: 2516

Title of Project: The Effect of Amplification on Limited High-Frequency Hearing Loss

Investigators:

Principal: Rauna K. Surr, M.S.

Associate: Daniel M. Schwartz, Ph.D.

Objectives: Assessment of California Consonant Test (CCT) as a clinical tool.

Technical Approach: Experimental hearing aid evaluations are now being scheduled for the final phase of this project. V.A. contract aids as well as a new ear level aid with extended high frequency amplification are being used. California Consonant Test (CCT) in quiet and in noise is the primary test for assessment of the effect of amplification.

Progress & Results: The two pilot studies mentioned as papers to be presented in the last interim report have been accepted for publication. A third pilot study for this project is near completion and has been accepted for presentation at the American Speech and Hearing Association Convention in November 1978 in San Francisco. These data show excellent test-retest reliability in soundfield presentation mode at various message-to-competition ratios for normal as well as hearing impaired subjects. Further analysis on split-half reliability is in progress.

Conclusions: Valuable information on clinical use of CCT has been obtained and we are now ready to proceed to the final phase of this project which is to use CCT in experimental hearing aid evaluation on persons with limited high frequency hearing impairment.

Funds Utilized: FY-77: Travel to Chicago, ILL, in November 1977 for paper presentation.

Funding Requirements: FY-78: Travel: Presentation of paper in San Francisco, November 1978 (copy of acceptance letter attached).

Publications: Schwartz, D.M., Surr, R.K.: Three Experiments on the California Consonant Test, J. Speech Hear Disord. November, 1978. Schwartz, D.M., Surr, R.K., et al: Performance of High Frequency Impaired Listeners with Conventional and Extended High Frequency Amplification, (inpress) by Audiology.

Type of Report: Interim

AMERICAN SPEECH AND HEARING ASSOCIATION
 1001 Nashville Ave.
 Nashville, Tenn. 37203
 (615) 257-5100

To: Rauna K. Surr
 Army Audiology & Speech Center
 Walter Reed Army Medical Center
 Forest Glen (156)
 Washington, D.C. 20012

From: Lyle L. Lloyd, Ph.D., Chairman, 1978 Convention Program Committee

Following the review process described on the enclosed memo, the 1978 Program Committee has directed me to inform you that your proposal, (ASHA # 781),

Sound Field Noise Interference Functions for the California Consonant Test

has been accepted as a Traditional Platform Presentation and is scheduled for:

Date Nov. 20 Time 3:45 Hotel & Room St. Francis-Elizabethan A&B

Your Session Chairman is: Gerard Kupperman - Univ. of Massachusetts

Unless otherwise indicated above, the maximum time available for Traditional Platform presentation of a Scientific/Technical paper is ten (10) minutes. The time for Miniseminars and for Poster Sessions is 90 minutes. Specific suggestions for your format are included.

Audiovisual equipment available in Traditional Platform and Miniseminar presentation rooms will include:

- a. chalkboard
- b. pointer
- c. a single microphone (if room is large enough to require amplification)
- d. 5 x 5 cm (2 x 2 in.) slide projector
- e. overhead projector, audio tape recorder and/or other special equipment requested on original proposals and approved for this session are as follows:

Since all Convention correspondence goes only to the First Author of multiple-authored proposals, would you please notify your co-author(s) (if any) of the acceptance of your proposal and of the details regarding its presentation.

Traditional Platform paper presenters should forward a copy of their paper to the Session Chairman at the earliest possible time.

We are grateful to you for your participation in this year's convention, and we hope the enclosed information will help you to understand the operation of the session in which you are scheduled.

See you in San Francisco!

Enclosures

MS, TP P & C

WORK UNIT NUMBER: 2517

TITLE: Evaluation of a Specialized Technique for Training Audiovisual Integration in Hard-of-Hearing Patients

INVESTIGATORS: Principal: Allen A. Montgomery, Ph.D.
Associate: Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

OBJECTIVE: This study is designed to evaluate the effectiveness of a newly-developed training procedure for improving patients' ability to use the audible and visible aspects of speech simultaneously.

TECHNICAL APPROACH: This study was divided into two parts.

Part I: Evaluation of Test Materials. To evaluate the effectiveness of a therapeutic technique it is necessary to have stable measures of the behavior under treatment. Part I was devoted to establishing the adequacy of three types of speech materials for pre- and post-testing. The sensitivity of the materials as derived from intelligibility-S/N functions and the reliability of the materials in a test-retest paradigm were determined with normal and hearing impaired subjects. Further, the equivalency of various forms of each test have been established.

Part II: Evaluation of Treatment Procedure: Part II of this study will follow a standard pretest, treatment-posttest paradigm with an experimental group receiving training in AVI and a control group not receiving training in AVI.

a. Subjects: The subjects in Part II were 30 hearing-impaired patients from the inpatient Aural Rehabilitation Program in the Army Audiology and Speech Center. The patients will be assigned randomly to experimental and control groups of 15 patients each.

b. Materials: The pre- and post-training materials and procedures developed in Part I of this study will be employed.

c. Procedure: The pre- and post-training testing were conducted on all patients to obtain measures of their ability to utilize simultaneously the auditory and visual components of speech prior to and following training (or following a comparable period of nontraining for the control group).

The training in AVI was done individually without noise in ten one-hour sessions employing a two-room environment. The training was done by audiologists and speech pathologists who will rotate assignments

such that no patient receives more than one half of his sessions from any one of the clinicians.

d. Data Analysis: The primary analysis involves the comparison of mean pre- and post-test results for the control and experimental groups. In addition, analyses is made of the learning curves of individual patients and of the errors on test items to provide insight into the nature of the learning which has taken place and the effects of training.

PROGRESS AND RESULTS: Part I, concerned with evaluation and development of test materials, is essentially complete. We have developed a useful and reliable test of audio-visual speech reception for use with hard-of-hearing patients. This test, based on the "Drill Sargent Passage" has demonstrated test-retest reliability of $r = 0.85$ with minimal learning taking place.

Part II of the study, which uses the test to evaluate the effectiveness of our specialized training procedures, is nearing completion. We have trained 12 of the 15 patients needed for the experimental group and tested eight of the 15 control patients. The results to date indicate that the technique is quite successful in improving the experimental patients' ability to perceive speech in noise, with improvement averaging 17% following training. In addition, the patients' reaction to the technique is quite favorable.

Our plans are that the new technique will be incorporated into the clinical routine of the Aural Rehabilitation Section on an experimental basis. Its effectiveness and its role in the overall program will continue to be monitored there, under our guidance. We are waiting until the transfer of the Army Audiology and Speech Center to the New Treatment Facility is complete before implementing the technique.

CONCLUSIONS: At the present time the technique appears to be beneficial to the patients and easy to administer. Final conclusions and recommendations will be made following a clinical trial in the Aural Rehabilitation Program.

FUNDS UTILIZED, FY-78: None

FUNDS REQUESTED, FY-79: None

PUBLICATIONS: The following papers, arising from this project, have been presented. In addition, an article is in preparation for submission to the Journal of the Academy of Rehabilitative Audiology.

Montgomery, Allen A. Research on Auditory-Visual Integration for Adult Hearing Aid Users. (Paper presented at Academy of Rehabilitative Audiologists Summer meeting, 1977. A summary of the proposed study was presented, and the technique was demonstrated.

Montgomery, Allen A. Assessment of a New Auditory-Visual Training Technique. (Paper presented at American Speech and Hearing Association annual convention, November 1977).

Montgomery, Allen A. Techniques for Training Auditory-Visual Integration. (Paper presented at National Technical Institute for the Deaf Research Seminar, Rochester, N.Y., November 1977).

TYPE OF REPORT: Interim

WORK UNIT NUMBER: 2518

TITLE: The Effects of Analytic Training on the Sentence Recognition
Ability of Hearing-Impaired Soldiers

INVESTIGATORS: Principal: Brian E. Walden, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

OBJECTIVE: The purpose of this investigation is to determine the effects of analytic lipreading and auditory training on the ability of hearing-impaired soldiers to recognize sentences audiovisually.

TECHNICAL APPROACH: The subjects of this investigation were 30 hearing-impaired soldiers selected from the inpatient Aural Rehabilitation Program of the Army Audiology and Speech Center. 20 of these subjects were assigned at random to two experimental groups of 10 subjects each, designated as the auditory and visual groups. The remaining 10 subjects constituted a control group. All subjects were administered a variety of test materials before and after a two-week training period. Test materials consisted of a 400-item test of auditory and visual consonant recognition and a 50-item test of audiovisual sentence recognition. Each of the tests were recorded on videotape and presented under controlled conditions to the subjects. The training materials consisted of 38 exercises designed to improve consonant recognition ability. The 38 exercises were graduated in difficulty with the earlier exercises having fewer consonants and only those which were easily identified by the hearing-impaired soldiers. Later exercises included a larger number of consonants many of which were frequently confused by the subjects.

Subjects in the auditory group received a test of auditory consonant recognition and the auditory-visual sentence test before and after two weeks of analytic auditory training. Subjects in the visual group received a test of visual consonant recognition and the audiovisual sentence test before and after two weeks of analytic lipreading training. The other 10 subjects constituted a control group and received the standard two-week group-oriented Aural Rehabilitation Program but did not receive any analytic auditory or lipreading training.

PROGRESS AND RESULTS: The results of the 400-item videotaped tests were organized into confusion matrices for each subject group. Separate matrices were prepared for the pre-training and post-training test results. These matrices are currently being analyzed to determine the effects of training on phoneme perception. The overall correct recognition score for the 50-item sentence test has been compared for the pre-training and post-training administrations for each group. This comparison suggests that the analytic training has a substantial beneficial effect on the audiovisual sentence recognition ability of both experimental groups. The amount of improvement,

however, is comparable for both groups suggesting that neither analytic auditory training or analytic lipreading training is superior to the other in improving audiovisual sentence recognition ability. The results for the control group of 10 subjects reveal that they also show improvement in audiovisual sentence recognition ability as a result of the standard Aural Rehabilitation Program. The magnitude of this improvement, however, is approximately half that of the experimental subjects receiving the analytic training.

CONCLUSIONS: The results to date suggest that analytic auditory and lip-reading training have a substantial beneficial effect on audiovisual sentence recognition ability, at least on a short-term basis. Neither training modality appears superior to the other in terms of its beneficial effect. Since the control group shows substantially less improvement than the experimental groups, it is apparent that the improvement in audiovisual sentence recognition ability of the experimental groups cannot be attributed to the effects of experience in hearing aid usage.

FUNDS UTILIZED, FY-78:

FUNDS REQUESTED, FY-79: None

PUBLICATIONS: The results of this experiment are to be presented at the Annual Convention of the American Speech and Hearing Association in San Francisco, November 1978.

TYPE OF REPORT: Interim

WORK UNIT NO.: 2519

TITLE: An Investigation of the Effects of Several Competing Signals on Aided Hearing Performance

INVESTIGATOR: CPT Donald R. Bender, Ph.D.

OBJECTIVE: To evaluate the effects of different types of competing signals when utilized as secondary sources in hearing aid evaluations. Specifically, the purpose of this investigation was to determine whether a particular noise when presented in conjunction with CNC monosyllabic word lists is an effective indicator of optimum amplification.

TECHNICAL APPROACH: The subjects in this study were eighteen adult males with bilateral sloping high frequency sensorineural hearing loss of moderate to severe degree. All subjects were considered appropriate candidates for a hearing aid as determined via prior pure tone and speech tests. The University of Maryland recording of CNC word discrimination lists was the stimulus of interest. Three competing signals (low-pass filtered noise, speech spectrum noise and speech babble) were presented at the signal-to-noise ratios of 0 and -5 dB. The competing signals were presented in an uncorrelated fashion from four loudspeakers located in a semi-circular fashion about the subjects while the primary stimulus was presented from a loudspeaker located directly in front of the subject.

The subjects were tested in three sessions. Each session lasted approximately one and one-half hours. The same stimulus and noise presentation format was utilized in the first and second experimental session with the exception that one of the two signal-to-noise ratios (0 and -5 dB) was alternately utilized in each session. The third session was included as a test of reliability and alternately replicated the first and second sessions. The presentation order of the word discrimination lists as well as the three noise sources was systematically varied within and between subjects to reduce order effects. Each subject received one CNC list in the presence of the three competing signals unaided and then through each of three hearing aids.

PROGRESS AND RESULTS: All phases of this experiment have been completed with the exception of the preparation of the final manuscript for publication. Analysis of data revealed several significant findings. Although considerable intersubject variability was evidenced in the individual word discrimination scores, mean performance did substantiate specific trends. Speech spectrum shaped noise and speech babble noise caused greater degradation in aided word discrimination ability in comparison to low-pass filtered noise.

Statistical analysis of group data failed to demonstrate meaningful differences in the overall performance among hearing aids in the presence of the three different noise sources. Inspection of individual performance, however, indicated that the subjects demonstrated greater reliability in selecting specific

hearing aids in the speech spectrum noise condition at the -5 dB signal-to-noise ratio. The test-retest agreement for speech spectrum noise was 78 percent whereas the other noise conditions demonstrated low reliability in rank ordering performance. The degree of consistency with which the poorest performing hearing aid was identified in the speech spectrum noise condition indicated that a hearing aid by competing noise interaction existed.

The magnitude of change or improvement from unaided to aided word discrimination ability across noises and signal-to-noise conditions was fourteen percent or less for all three hearing aids. These results were consistent with performance observed in clinical settings with the particular hearing loss population.

Statistical analysis indicated that the presentation order of signal-to-noise ratios did not significantly influence the results of this investigation. Further statistical analysis indicated that a significant amount of learning had occurred. In light of the amount of exposure to the stimulus and the subject's adaptation to amplification, a modest amount of learning (4.5 percent) was observed.

CONCLUSIONS: In analyzing the results of the study, the following conclusions are warranted:

1. In all three competing signals, the less favorable signal-to-noise ratio produced a more deleterious effect upon word discrimination ability than did the more favorable signal-to-noise condition. These results reinforce the concept that discrimination ability in the presence of competing signals is dependent upon the degree of competition offered by the secondary signal.

2. No significant differences were observed in the overall performance of the three hearing aids in the presence of the three competing signals. When individual aided performance (rank ordering) was examined, specific noise by hearing aid interactions were in existence.

3. Speech spectrum shaped noise at the -5 dB signal-to-noise ratio demonstrated the highest degree of reliability in determining optimal amplification, that is, a test-retest agreement of 78 percent in rank ordering hearing aids.

4. Although preliminary results demonstrate a high reliability index for speech spectrum shaped noise at the -5 dB signal-to-noise ratio, a verification of this reliability on a larger clinical sample is required before a recommendation for general clinical application can, as should be offered.

FUNDS UTILIZED FY-78: None

FUNDS REQUIRED FY-79: None

PUBLICATIONS: A manuscript describing this research is being prepared for submission to the Journal of Speech and Hearing Research.

TYPE OF REPORT: Completed

Work Unit No.: 2520

Title of Project: The Effect of the Change of Body Position on Nystagmus during Electronystagmography (ENG)

Investigators:

Principal: Ms. Sylvia K. Allen, M.A.

Associate: Mrs. Rauna K. Surr, M.S.
Mrs. Nan K. Lukmire, M.Ed.

Objectives: To measure how sudden shifts in patient position during the ENG procedure may induce or alter nystagmus. To correlate this nystagmus with vestibular pathology.

Technical Approach: Testing is done in conjunction with routine patient referral for ENG. After regular procedures and initial evaluation of results, one additional caloric stimulation is done. During period of nystagmus, patient's position is changed from supine to prone and back to supine. Nystagmus is recorded and correlated with standard nystagmus and vestibular pathology.

Progress and Results: Ms. Allen, principal investigator, above, left Walter Reed Army Medical Center this year. While some preliminary data may have been collected in FY-77-78, it is no longer available. The study is in the process of being begun anew with Mrs. Surr and Mrs. Lukmire, above, as principal and associate investigators, respectively.

Conclusions: None at this writing.

Funds Utilized, FY-78: None

Funding Requirement, FY-79: None

Publications: None

Type of Report: Interim

WORK UNIT NUMBER: 2521

TITLE: Reaction Times of Stutterers and Nonstutterers

INVESTIGATORS: Principal: Robert A. Prosek, Ph.D.
Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVES:

- a) To determine if the reaction times of stutterers and non-stutterers differ from each other for a variety of speech and nonspeech tasks.
- b) To determine if the speech reaction times of stutterers and nonstutterers differ from each other with respect to the onset of laryngeal EMG activity.
- c) To determine the effects of training on the reaction times of stutterers and nonstutterers.

TECHNICAL APPROACH: Ten stutterers and ten nonstutterers, matched for age and sex, perform nine reaction time tasks, each of which is repeated on five consecutive days. Each task represents a combination of one of three stimuli and one of three responses. The three stimuli are a light flash, a 1000 Hz pure tone, and a vowel-consonant (VC) monosyllabic word. When the button push is the response, reaction time is defined as the time elapsed between the onset of the stimulus and the onset of the button push. When the tongue click is the response, reaction time is defined as the time elapsed between the onset of the stimulus and the onset of the tongue click as measured by a microphone and voice actuated switch. When the VC monosyllables are the response, two reaction times are defined: 1) Acoustic reaction time is the time elapsed between the onset of the stimulus and the onset of the word as measured by the microphone and voice switch, and 2) Laryngeal reaction time is the time elapsed between the onset of the stimulus and the onset of the laryngeal EMG activity associated with the production of the VC word as measured by bipolar surface electrodes placed over the cricothyroid regions.

The primary data analysis technique will be a four-factor analysis of variance in which the factors are (1) groups (stutterers and nonstutterers), (2) stimulus (light, tone and word), (3) response (button push, tongue click, acoustic reaction time and laryngeal reaction time), and (4) training (five repetitions of each task).

PROGRESS AND RESULTS: Pilot studies have been conducted to determine if the procedures and equipment used will meet the objectives of the study. On the basis of these studies, two changes have been made in the procedures used to obtain data.

First, in one task, the subject is required to repeat a VC word as quickly as possible. Only two words were used, "ape" and "Abe," which differ only in the final consonant. It was found that the pilot subjects

would begin producing the vowel portion of the word before the stimulus was completely presented. As a result, extremely low reaction times were being recorded. When the number of VC stimuli was increased to 16, it was found that the subjects were forced to listen to the entire word in order to respond correctly. Therefore, the VC ensemble will be increased to 16 words.

Second, a spectrographic analysis of the subjects' VC responses was to be made to determine if voicing offset differences existed between stutterers and nonstutterers. It was found that the vowels recorded were of very short duration and that the final consonants were likely to be absent or in error. Since it is doubtful that this analysis will provide a definitive answer to the question of voicing offset differences, the experiment will concentrate on the onset of the responses.

CONCLUSIONS: Not applicable at the present time.

FUNDS UTILIZED, FY-78: \$500.00

FUNDING REQUIREMENTS, FY-79: \$2,500.00 (for the digital counter/printer as specified in the original protocol.)

PUBLICATIONS: Not applicable at the present time.

TYPE OF REPORT: INTERIM

WORK UNIT NUMBER: 2522

TITLE: Monaural Versus Binaural Amplification for Hearing Impaired Listeners

INVESTIGATORS: Principal: Daniel M. Schwartz, Ph.D.

Associate: Nan K. Lukmire, M.Ed.
Allen A. Montgomery, Ph.D.
Robert A. Prosek, Ph.D.
Brian E. Walden, Ph.D.
Roy K. Sedge, MAJ, MSC, Ph.D.

OBJECTIVES: To determine the efficacy of binaural hearing aids for improving word and sentence recognition in noise for hearing impaired listeners.

TECHNICAL APPROACH: Each subject is seated in the center of a sound treated test booth facing a loudspeaker positioned directly in front of the listener. The subject is then instructed to adjust his hearing aid to a comfort level setting while listening to a multi-talker speech babble. This volume control setting is then marked on the hearing aid. Next, the listener is instructed to do the same task of comfort level adjustment while wearing two (binaural) hearing aids. Here again, the volume control setting of the two hearing aids were marked for future comparison.

For the test procedure subjects are required to respond in writing to recorded monosyllabic words and sentences presented through a loudspeaker directly in front of the listener in quiet and in the presence of a multi-talker speech babble which is presented through four additional loudspeakers located to each side, the back and overhead of the listener in an effort to achieve a "cocktail party" effect. This procedure is then repeated while the subject is fitted with two identical hearing aids.

The subject is retested under the same experimental conditions one week following the initial session. In the interim, an electroacoustic response of each hearing aid is obtained with the volume control set as per the subject's adjusted level.

PROGRESS AND RESULTS: To date only five subjects have been run since few subjects have met the criteria for hearing loss configuration necessary for inclusion in this study. Data for the five subjects do not show marked differences in performance between monaural and binaural conditions.

CONCLUSIONS: Not applicable at this time.

FUNDS UTILIZED, FY-78: None

FUNDING REQUIREMENTS, FY-79: \$1,200.00 for 3 cassette tape recorder/players.

PUBLICATIONS: Not applicable at the present time.

TYPE OF REPORT: Interim

WORK UNIT NUMBER: 2523

TITLE: The Relationship Between Electroacoustic Parameters and Perceived Sound Quality of Hearing Aids

INVESTIGATORS: Principal: Daniel M. Schwartz, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Robert A. Prosek, Ph.D.

OBJECTIVES: To determine the relationship between various perceptual dimensions and physical characteristics of hearing aids in judging the sound quality of hearing aid amplified speech.

TECHNICAL APPROACH: A 20 second passage from the book "Tom Sawyer" was recorded through 20 different hearing aids mounted on a Knowles Electronics Maniken for Acoustics Research. In addition, 17 measures of the electroacoustic characteristics of each hearing aid were obtained as the aid was mounted on the maniken.

The hearing aid recorded speech samples from each of the 20 hearing aids were then paired with every other hearing aid and spliced onto a master tape resulting in 190 pairs of hearing aid recorded speech.

Ten normal hearers and 10 hearing impaired listeners listened to the hearing aid recorded speech samples as transduced through an insert receiver having a flat acoustic spectrum through 10,000 Hz. Each listener was seated in a sound-isolated test room and was presented with a two position switch which allowed him to hear a speech sample recorded through each pair of hearing aids. The subject was instructed to judge which of the two hearing aids in each of the 190 pairs he preferred on the basis of sound quality. Second, each listener was required to judge how similar the two hearing aids were with respect to sound quality and to rate similarity on a seven point equal appearing interval scale.

Data for each subject were collected in three separate test sessions in an effort to determine the reliability and consistency of both the preference and similarity ratings. That is, each subject judged the similarity and preference of 190 pairs of hearing aids on each of three test sessions.

PROGRESS AND RESULTS: Data have been obtained on all normal hearing and hearing impaired subjects and data reduction and analysis is presently in progress. The PDP-11 computer has been programmed for INDSCAL analysis for organizing the data into similarity matrices and for correlating the coordinates of the stimuli in the multidimensional space to those from the 17 electroacoustic characteristics of each hearing aid.

CONCLUSIONS: Not applicable at the present time.

FUNDS UTILIZED, FY-78: None

FUNDING REQUIREMENTS, FY-79: \$17,000.00 (for FRY ELECTRONICS MODEL 10,000 Hearing Aid Analyzer).

PUBLICATIONS: Results of this experiment are to be presented at the annual convention of the American Speech and Hearing Association, San Francisco, California, November 1978.

TYPE OF REPORT: Interim

WORK UNIT NUMBER: 2524

TITLE: The Effects of Assertiveness Training on Hearing Impaired Soldiers

INVESTIGATORS: Principal: Allen A. Montgomery, Ph.D.
Associate: Suzanne K. Sedge

OBJECTIVE: To determine the effects of assertiveness training on the levels of assertiveness and self-concept in hearing impaired soldiers.

TECHNICAL APPROACH: Hearing impaired patients from the two-week Aural Rehabilitation Program are assigned to either a control group which receives only traditional rehabilitative techniques, or to an experimental group which receives communication-centered assertiveness training as well as aural rehabilitation. Evaluation of the effectiveness of the assertiveness training is performed by administering two standardized tests, the Adult Self-Expression Scale and the Tennessee Self-Concept Scale, at the beginning and end of the training period, as well as by debriefing patients and therapists. Standard descriptive and correlation techniques and the analysis of variance are used to analyze the results.

PROGRESS AND RESULTS: The assertiveness training program has been designed and tested, and data collection on both control and experimental groups is complete. Data analysis is in progress. At the present time it appears that the control group showed little or no improvement in either assertiveness or self-concept, while the experimental group demonstrated significant gains on both measures. Both groups of patients show high test-retest reliability, and the results of the post-training tests are in good agreement with the information from the debriefings.

CONCLUSIONS: Until the statistical analyses are complete, no firm conclusions can be drawn.

FUNDS UTILIZED, FY-78: None

FUNDING REQUIREMENTS, FY-79: Supplies - \$100.00

PUBLICATIONS: N/A

TYPE OF REPORT: Interim

WORK UNIT NUMBER: 2525

TITLE: Generation and Evaluation of Synthetic Facial Images for Studying and Training Lipreading

INVESTIGATORS: Principal: Allen A. Montgomery, Ph.D.
Associate: Brian E. Walden, Ph.D.
Robert A. Prosek, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVE: This study is designed to evaluate the feasibility of simulating on a computer graphics system, the information-bearing elements of the talker's mouth and face during speech, for the purpose of studying lipreading in hard-of-hearing patients.

TECHNICAL APPROACH: The first year of this study could be thought of as "mastering the medium." This effort centers around a comparison of natural (videotaped) images and computer-reproduced images of talkers' faces during speech. To insure a high quality, realistic computer-reproduced image, the videotapes of real talkers will be handcopied as line drawings, frame-by-frame, and transferred to the graphic systems display memory. From here they may be displayed in animated form for evaluation and refinement. In essence, this procedure is a test of our ability to extract those elements that contribute to visual naturalness and intelligibility. The intelligibility will be evaluated through a detailed comparison of the recognition errors (confusions) produced by hard-of-hearing patients lipreading the natural videotaped speech and the computer-displayed speech.

The stimuli will be prepared for computer reproduction by hand tracing the individual videotape frames from a 20" TV monitor driven by a Panasonic NU-3160 videotape recorder with still frame and slow motion capability. The traced images of the talker's lips and jaw (actually, anything that moves) will be transferred to the display memory of a Tektronix Model 4081 computer graphics system via a Model 4954 digitizer and stored on floppy disc memory in sequential files after editing. The files will then be available for reproduction at 30 fps in association with an immobile "upper 1/2 face" to form an animated facial image on the system's 19" CRT display. Obvious errors and discontinuities will be corrected and considerable informal manipulation of the images will be done to discover the essential visual elements of the talkers' faces and to eliminate those elements that are redundant and not necessary for naturalness or artistic acceptability of the image.

PROGRESS AND RESULTS: The first two months of this project have centered on developing the software necessary to display animated facial images. Subroutine PLTOBJ, which takes images traced from the TV monitor and transforms them into a form appropriate for rapid sequential display, has been written and debugged. Program ANIMAT which controls the rate

and duration of display and puts several graphic parameters at the experimenter's command is now in the final stages of development. In addition, a master videotape recording of a talker producing CV monosyllables and audiometric test words has been made and is being prepared for frame-by-frame tracing.

CONCLUSIONS: N/A

FUNDS UTILIZED, FY-78: None

FUNDING REQUIREMENTS, FY-79: Travel - \$675.00
Equipment - \$5,571.00
Supplies \$580.00

PUBLICATIONS: N/A

TYPE OF REPORT: Interim

Work Unit No.: 2601

Title of Project: In Vitro and In Vivo Properties of Sensitized Lymphocytes in Transplantation Immunology.

Investigator: Everett K. Spees, COL MC

Objectives: The objectives of this project were broad ones of developing improved methods of transplantation, organ preservation, and immunosuppression; and, to study the kinetics and mechanisms of immune responses.

Technical Approach: Patients and volunteer control subjects are skin tested with DNCB and observed for their capacity to develop cutaneous hypersensitivity reactions to this chemical. In vitro assays are done to ascertain the activation-proliferative responsiveness of the patients' lymphocytes to this same haptenic antigen.

Basic transplantation immune mechanisms are studied in experimental animal models. Islet of Langerhans allografts in diabetic rats were used for this purpose in this past year.

Progress and Results: Good progress was made in refining and standardizing an in vitro assay for DNCB responsiveness. 26 patients and volunteers were tested. While those whose lymphocytes were nonresponsive in the in vitro cultures failed to develop delayed hypersensitivity reactions, many of those studied had appreciable lymphocyte proliferative responses while at the same time being skin test negative.

The mechanisms of immunologically mediated rejection of islet cell allografts was studied. Briefly, islets were found to be much more sensitive to antibodies (humoral immunity) than are other transplantation models; to be rejected, in untreated animals, very rapidly (within 3 to 5 days) by a cell mediated mechanism- before normal cellular immunity could be expected to develop; and therefore islet allografts are presumably destroyed by preformed killer cells- probably the so called M-lymphocytes.

The principal investigator for this work unit retired from the U.S. Army one year ago and it is recommended that this project be terminated.

Conclusions: Many negative skin tests to DNCB in patients with renal failure are so because of depressed capacities in developing nonspecific inflammatory responses rather than because antigen specific lymphocytes are not activated and sensitized by DNCB-carrier complexes.

Allogenic pancreatic islet cell implants are probably often rejected by preformed effector lymphocytes before normal humoral or, more importantly, cellular immunity can develop.

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications, FY-78: Oakes, D.D., Spees, E.K., Annable, C.R., and Reckard, C.R. Acute Hepatocellular Damage following Intraportal Transplantation of Pancreatic Islets in Rats. J. Surg. Res. 24: 182, 1978.

Type of Report: Terminated

Work Unit Number: 2610

Title: Antilymphocyte Globulin and Kidney Transplantation: A Controlled Double Blind Study.

Investigator: Jimmy A. Light, COL MC

Objective: To define the value of antilymphocyte globulin in clinical transplantation.

Technical Approach: Not applicable

Progress and Results: This protocol, approved in 1973, has never been implemented. It has been carried in an inactive status pending the availability of a suitable ALG for use in this project. The study purposed, although original in design at the time of its inception, is now in progress or has been completed at a number of transplantation centers. In its present form it is no longer a useful protocol. However, it continues to provide a useful background in information for the clinical use of antilymphocyte globulin. With the recent amalgamation of the Army and Navy organ transplantation services and with a well controlled source of ALG from the Naval Research Laboratories becoming available, there is a good possibility that this protocol or a modification of it may be implemented within the coming fiscal year. It is therefore recommended that the protocol continue to be carried in an inactive status pending the development of a joint program with the Navy as mentioned above.

Conclusions: Not applicable.

Funds Utilized, FY-78: None.

Funding Requested, FY-79: None.

Publications, FY-78: None.

Type of Report: Interim

Work Unit No.: 2611

Title: Survey of Multiparous Patients for Anti HL-A Antibodies

Investigator: Everett K. Spees, COL MC

Objective: The objective of this project is to survey multiparous volunteers for HLA antibodies suitable for reagent use.

Technical Approach: Standard modified Amos and NIH microcytotoxicity serologic typing of multiparous volunteers from the Greater Washington Area would be done in order to ascertain whether or not any given person had monospecific antibodies to one of the human histocompatibility antigens

Progress and Results: No work was completed on this project because personnel (technician) positions have not been filled during the past fiscal year. In addition, the principal investigator for this work unit retired from the U.S. Army a year ago.

Conclusions: Not applicable

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications: None

Type of Report: Terminated

Work Unit No.: 2614

Title of Project: HLA Tissue Typing Studies on an Alaskan Population Group, and a Possible Relationship to Organ Transplantation Science.

Investigators:

Principal: Everett K. Spees, Jr, COL MC

Coinvestigators: Gary B. Clark, LTC MC, Chief, Pathology Svc, MEDAC, Ft Wainwright, Alaska; Frederick A. Milan, PhD, Department of Anthropology, Univ of Alaska, Fairbanks, Alaska; Valerie Henson, ASCP, Supervisory Technologist, Organ Transplant Svc, WRAMC.

Objective: To study the HLA tissue types of an isolated American population in order to obtain new information on the biomedical role of this genetic system, and to apply this to organ transplantation science.

Type of report: Termination

Primary investigator resigned Aug 77. There was no action on this protocol in FY-78. Protocol should be terminated.

Work Unit Number: 2615

Title: Immunological Monitoring of the Transplant Recipient

Investigators: Jimmy A. Light, COL MC
Charles R. Annable, COL MC

Objective: The objective of this project is: 1. to assess the general and donor specific immunological responsive capacity of prospective renal transplant recipients, 2. to evaluate graft recipients for impending or ongoing rejection reactions, and 3. to monitor the effects of immunosuppressive drugs on immune responsiveness.

Technical Approach: A panel of ten different in vitro immunological assays are performed in a serial manner prior to and over a prolonged period following organ transplantation.

Progress and Results: Tests on 43 patients have been done this year. Progress in establishing standardized and reliable in vitro assays has been quite good despite an unusual turnover in technicians working on this project. Tentative conclusions being made from the results obtained are outlined below.

Conclusions: Partially substantiated conclusions and working hypotheses that are continuing to be used are as follows: 1. Impending and ongoing allograft rejection reactions can be discerned by serial assays of peripheral blood mononuclear leukocyte spontaneous blastogenic activity and by noting any appreciable decline in the percentage of active SRBC rosetting T-lymphocytes. The laboratory monitoring of immunologically mediated rejection reactions can probably be made with an even higher degree of certainty if quantitative determinations of serum C-reactive protein and beta 2-microglobulin are also performed. Antibody mediated reactions are noted by antibody dependent cellular cytotoxicity and complement dependent cytotoxicity assays. 2. In addition to the established practice of matching donors with recipients with the aid of immunogenetic studies, measurements of the general immunological capacities or overall immunocompetence of an allograft recipient are importantly linked to the probable success or failure of a transplantation procedure. Of the assays presently performed the relative reactivity of the patients lymphocytes in mixed lymphocyte cultures and their responsiveness to nonspecific mitogens are indicative of immune capacity. A firmer assessment of immunocompetence can probably be obtained by also measuring in vitro responses to specific new and recall antigens (e.g. DNCB, SKSD, PPD, and tetanus). 3. Determining the effects of immunosuppressive drugs is again a problem of measuring general immune capacities and the tests noted in item 2 seem to be best suited for this purpose. However results to date indicate that mitogen responses after two to four weeks of therapy are not reliable determinants of immunosuppression.

Funds Utilized, FY-78: 37,217

Funding Requested, FY-79: 38,000.

Publications: FY-78: None

Type of Report: Interim

Work Unit No.: 2616

Title: Obviating the Graft-Versus-Host Reaction

Investigator: Charles R. Annable, COL MC

Objectives: The central objective of the experiments, being done to fulfill the goals of this work unit, is to manipulate the naturally occurring physiological phenomenon that takes place following the stimulation or activation of the immune system in such a manner that bone marrow transplantation across major histocompatibility barriers can be carried out without incurring a graft versus host reaction. This requires a functionally complete mobilization from the bone marrow of a donor of the small subpopulations of lymphocytes that are activated by, and that can subsequently react destructively against, the given histocompatibility antigens of a prospective recipient-host.

Specific objectives, that were achieved over the past year, were to determine in a standardized graft versus host animal model whether or not the specific lymphocytes responsible for this reaction can be mobilized from the bone marrow with an appropriate immunization procedure.

Technical Approach: Standard graft versus host reaction animal experimental models are utilized to carry out these studies. Inbred strains of rats are used.

Progress and Results: The kinetics of deletion of antigen specific lymphocytes from lymph nodes and the bone marrow has been delineated. It has been found that, with adequate antigen exposure, cellular preparations from both the bone marrow and the lymph nodes will not elicit a graft versus host reaction when the lymphoid tissues are harvested 24 to 48 hours following specific immunogenic stimulation. In addition, by taking advantage of these findings, nine lethally irradiated animals have now undergone successful allogeneic bone marrow transplantation without developing secondary disease or graft versus host reactions.

Conclusions: Specific antigenic stimulation can result in a complete mobilization of reactive lymphocytes from the bone marrow (and lymph nodes) by 24 to 48 hours following the immunization procedure. It can now tentatively be concluded that successful bone marrow transplantations can be done without incurring a graft versus host reaction.

Funds Utilized, FY-78: 21,820

Funding Requested, FY-79: 17,500

Publications: None

Type of Report: Interim

WORK UNIT: 2703

TITLE OF PROJECT: Exclusive Use of Autologous Blood Transfusions in
Elective Thoracic & Open Heart Surgical Procedures

INVESTIGATORS:

Principal: Arthur W. Fleming, M.D., LTC, MC

Associates: Walter H. Brott, M.D., COL, MC
John H. Radcliffe, LTC, MSC

OBJECTIVES:

1. To develop a systemic approach for obtaining a sufficient volume of autologous blood for use during and after elective thoracic and open heart surgical procedures, thus reducing the need for homologous blood transfusions.

2. To serve as a model for patients undergoing less hazardous surgical procedures.

TECHNICAL APPROACH:

See published report.

PROGRESS AND RESULTS:

The first publication from this work was published during FY 78 in the American Surgeon and was entitled "Development of a Practical Autologous Blood Transfusion Program." The response to this publication both from within WRAMC and at other institutions was mixed. There was general enthusiasm among blood bankers. However, there was still a considerable amount of hesitation on the part of individual surgeons who must share the responsibility for initiation of and carrying out such a program. The principal investigator has set on the American Association of Blood Banks National Committee for autologous blood transfusions for the past three years and has been very cognizant of the trend across the United States. As a consequence, during FY 78, our efforts were devoted toward trying to reduce the administrative and technical complexities that are possibly responsible for deterring some surgeons from using autologous blood transfusions for elective surgical procedures. It was apparent that at WRAMC we had taken patients who were of the greatest risk and had demonstrated that they could successfully donate blood for their own operations. It is now considered important to try to convince other surgeons of the multiple advantages inherent in an autologous blood transfusion program. We have subsequently written a second paper entitled "Design and Implementation of a Predeposit Autologous Blood Transfusion Program." This paper is in essence a "cookbook" so that any hospital or surgical service could initiate their own program with the aid of a blood

bank that wishes to cooperate. In addition, a paper entitled "Questions and Answers Concerning Autologous Blood Transfusions" has been written by the principal investigator for both professional and lay people. This paper was used in preparation of a brochure which has been widely circulated.

CONCLUSIONS:

The experience with patients on the Thoracic and Cardiovascular Surgery Service demonstrated that high risk patients tolerate donating multiple units of blood. In addition, a systemic approach for the procurement of multiple units of blood has been established. Our goal at this point is to expose all of the other surgical services to the technique that we have developed with the hope that patients who are of less a risk might routinely become autologous blood donors.

FUNDS UTILIZED FY 78: No funds were used during FY 78.

FUNDS REQUESTED FY 79: 0

PUBLICATIONS FY 78:

Fleming, A.W., D.C. Green, J.H. Radcliffe et al.: Development of a Practical Autologous Blood Transfusion Program. Amer. Surg. 43:794, 1977 (Dec).

Paper ready for submission: Fleming, A.W., D.C. Green, W.H. Brott et al.: Design and Implementation of a Predeposit Autologous Blood Transfusion Program (manuscript enclosed).

TYPE OF REPORT: Completed. Our objectives of developing a systemic approach for obtaining autologous blood as well as serving as a model for other surgical services has been realized. The thrust of our efforts for the future will be concentrated on exposing surgeons and blood bankers to the technique that we have established. Two exhibits have also been presented on this work:

1. Fleming, A.W., D.C. Green, D.M. St. James, J.H. Radcliffe, and P. Olson: An expanded use of autologous blood transfusion: An organizational approach. Exhibited at the American Association of Blood Banks Twenty-eighth Annual Meeting, Chicago, Illinois, November 9-14, 1975.

2. Fleming, A.W., D.C. Green, J. Radcliffe, and D.M. St. James: Development of a practical autologous blood transfusion program. Exhibited at the 45th Annual Assembly of the Southeastern Surgical Congress, Bal Harbour, Florida, April 3-7, 1977.

Type of Report: Completed

DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-SGU

SUBJECT

Work Unit #2804, An Evaluation of the Efficacy of Tadenan in the Treatment of Benign Prostatic Hyperplasia

TO

C, Clin Invest Svc

FROM

C, Urology Service

DATE

16 Oct 78

CMT 1

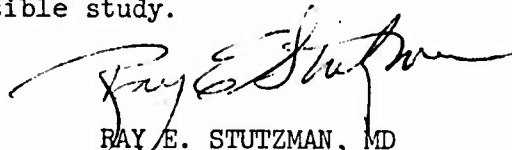
COL Stutzman/11s/62203

1. In reply to your correspondence reference the annual progress report on the clinical investigation program work unit #2804, An Evaluation of the Efficacy Tadenam in the Treatment of Benign Prostatic Hyperplasia, the following comments are in order.

a. This study has not been initiated at Walter Reed Army Medical Center in view of FDA regulations and criteria which we cannot at this time meet.

b. Phase 1 and Phase 2 studies are currently being performed in some civilian research centers and clinical application is not yet permitted.

c. It is requested that this project be continued on a "hold" basis until further information is obtained which will assist us in determining whether or not the project is in fact a feasible study.



RAY E. STUTZMAN, MD
COL, MC, USA
C, Urology Service

Work Unit No.: 2805

Title of Project: Biochemical Studies of Urinary Polyamines in Human Genitourinary Carcinoma.

Investigators: Nesbitt D. Brown, DAC, B.P. Doctor, PhD, S. Koetitz, DAC, and David G. McLeod, LTC MC.

Conclusions: We have developed a new methodology of extraction and measurement of urinary polyamines by a high pressure liquid chromatograph which allows lower operating pressures, reduced buffer flow and ease of operation. We have identified for the first time, two compounds in the urine of patients with carcinoma of the genitourinary system. Both of these compounds in addition to spermine, speridine and putrescine have been found to be elevated in our measurements of some patients with genitourinary carcinoma. We continue to have every reason to believe that these compounds may be utilized as tumor markers in the diagnosis, staging and prognosis of patients with genitourinary carcinoma.

Funds utilized FY-77: \$4,000

Funds requested FY-78:

Consumable supplies: \$4,000 (chemicals, reagents, enzymes and radioisotopes)

3,500 (columns and analytical small equipment)

2,000 (secretarial assistance and attendance at meeting)

Publications: A publication to the Journal of Chromatography is being prepared.

A paper was also presented at the annual Kimbrough Urological Meeting in Nov 78.

Type of Report: Interim

Work Unit No.: 2807

Title of Project: Determination of Human Prostatic Acid Phosphatase in Both Benign and Malignant Condition by Radioimmunoassay

Principle Investigators: W.D. Belville, M.D., MAJ, MC, D.E. Mahan, PhD, J.C. Clements, LT, MC, USNR, R.E. Stutzman, M.D., COL, MC, D.G. McLeod, M.D., LTC, MC, B.P. Doctor, PhD M.J. Gemski, J.E. Fowler, M.D., MAJ, MC

Co-Investigators: M.J. Raife, MD, MAJ, MC, R.B. Sweet, M.D., MAJ, MC, W.Babcock, M.D., MAJ, MC, C.F. Miller, M.D., MAJ, MC W.P. Duff, MAJ, MC

Objectives:

1. To establish the normal range of prostatic acid phosphatase in serum and bone marrow using RIA methodology. Completed.
2. To establish using radioimmune and enzymatic analysis the duration and magnitude of serum elevations of prostatic acid phosphatase following transurethral prostatectomy and prostatic massage. Benign group completed.
3. To assess the diagnostic usefulness of bone marrow acid phosphatase measurement by enzymatic and immunological procedures for confirmation of occult metastatic carcinoma of the prostate. See publications; two year follow-up in progress.
4. To continue the support (antibody) of a project entitled "Clinicopathologic Study of Prostate Tumors".
5. To evaluate the usefulness of the methodology for the medicolegal applicability involving rape.
6. To develop an alternate immunochemical procedure that avoids the use of radioactive pharmaceuticals. (ELISA)

Technical Approach: Serum and bone marrow aspirates from patients with and without prostatic carcinoma are evaluated for prostatic acid phosphatase

content using a quantitative immunochemical procedure. (See publication #3) The levels of prostatic acid phosphatase found in the bone marrow of patients with prostatic carcinoma are correlated with the presence of bony metastasis. (See publications 1 and 2).

Progress and Results:

1. More than 200 controls have demonstrated on upper limit of 8.1 ng/ml for serum and 12.0 ng/ml for bone marrow (97.5 percentiles).
2. We have established a consistent significant elevation of serum prostatic acid phosphatase following transurethral prostatectomy. By studying more than twenty patients all demonstrated at least a four fold elevation from the baseline during the study. Prostatic massage in benign prostatic hypertrophy has had no effect on the serum level. Currently patients with prostatic carcinoma are being studied. Recent literature has suggested diagnostic potential if a serum elevation is elicited.
3. Bone Marrow Results by Radioimmune Assay. To date we have determined by radioimmune assay the prostatic acid phosphatase content of more than 200 marrow aspirates obtained from patients with various stages of prostatic carcinoma. Up to ninety-six percent of those patients with proven bony metastatic (D_2) disease had elevated bone marrow prostatic acid phosphatase values. In patients with stages C and D_1 disease, 18 and 25 percent, respectively, had elevated bone marrow prostatic acid phosphatase values. We suspect that the elevations found in those patients with C and D_1 disease represent the detection of occult metastatic disease. A two year follow-up is currently being carried out to answer this question.

Funding Requested FY 1979

Personnel - GS 05 technician	\$ 9,303.00
Equipment	
Electrophoresis equipment	600.00
Supplies	
Pipets, disposable	200.00
Micropipet tips 20 x 30	600.00
Micropipets - 3	300.00
Centrifuge tubes 27 x 36	540.00
Test tubes and cords	300.00
Columns	150.00
Buffers	120.00
¹²⁵ Iodine 55 x 12	660.00
GARG 16 x 25	400.00
Human serum 27 x 50	1,350.00
Fetal calf serum 10 x 15	150.00
Travel	1,000.00
Other Computer services	800.00
	\$15,473.00

Publications

Enclosed is a publication that appeared in the June 1978 issue of Cancer. Also a draft of a paper currently in press in the Journal of Urology. A working draft of a paper in press in the Canadian Journal of Clinical Biochemistry is also enclosed.

Type of Report

Interim

Work Unit No.: #2809

Title of Project: Relationships between Prostatic Cancer and Excretion of Urinary Cholesterol.

Investigators:

Principle: Harry Y. C. Wong, Ph.D.

Associate: David G. McLeod, M.D.

Objectives: To develop a new biochemical test for the early diagnosis of prostatic carcinoma.

Technical Approach: Twenty-four hour urine samples were collected from forty American black males. These were analyzed by a modification of a gas liquid chromatography method reported by Vela and Acevedo (Steroids 14:499, 1969).

Progress & Results: Our preliminary studies indicate that the urinary NEC of thirteen healthy "normal" asymptomatic black Americans, ranging in age from 25-61 years, was within the normal limits for NEC of 0.10-1.20 mg/24 hr as observed by Vela and Acevedo. Four of seven males, clinically diagnosed as having benign prostatic hypertrophy, had NEC concentrations of 0.62-1.13 mg with three patients having values ranging from 1.33-1.53 mg. All seven patients with untreated prostatic cancer showed a hyper-excretion of NEC, ranging from 2.68-7.20 mg/24 hr. Ten of twelve subjects under treatment for prostatic carcinoma by either diethylstilbestrol radiation therapy or a combination of radiation treatment and bilateral orchidectomy had NEC levels within normal limits. However, two patients treated with DEC had NEC concentrations of 1.95 and 2.30 mg, respectively. It was observed that one subject with carcinoma of the prostate, who had a prostatectomy, had a NEC level of 0.68 mg.

Conclusions: Our preliminary findings indicate that there is an increase in the level of urinary NEC in all black patients with untreated prostatic cancer as compared to a lower concentration for subjects with benign prostatic hypertrophy. The "normal" healthy black males and most of the patients under treatment for prostatic carcinoma, with the exception of two subjects, were within normal limits. The urinary NEC levels may be useful in determining whether a patient is under control or not while being treated.

Funds Utilized, FY-78: None

Funding Requirements, FY-79:

Travel: \$1,000 - To attend a meeting and presentation of paper by Dr. McLeod

Publications: Relationship of Urinary Non-Esterified Cholesterol and Prostatic Cancer in Black Americans. 60th Endocrine Society Meeting #900, Miami, Florida, June, 1978. Paper is in preparation as manuscript.

Type of Report: Interim

Work Unit No.: 2810

Title of Project: Comparative Study of High Dose Versus Low Dose Preoperative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder.

Investigators:

Principal: David G. McLeod, MD

Urology Service, WRAMC
Duke University

Objectives: The purpose of this study is to determine whether moderate dose preoperative adjunctive radiotherapy plus radical cystectomy is as effective as low dose preoperative adjunctive radiotherapy plus radical cystectomy and pelvic node dissection in enhancing survival and prolonging the disease free interval, to determine the relative rates of tumor downstaging, the relative complication rates, the relative periods of hospitalization and time lost from work, (the relative cost of treatment selection), and the impact of delayed surgical treatment on the appearance of detectable metastatic disease.

Technical Approach: Patients are randomized to receive either high dose or low dose radiation therapy prior to radical cystectomy.

Progress and Results: Four patients have been entered into the study.

Conclusions: None at present.

Funds Utilized, FY-78: None

Funding Requirements, FY-79: None

Publications: None

Type of Report: Interim

Work Unit No.: 3102

Title of Project: Therapy of Immunodeficiency Diseases with Transfer Factor

Investigators: R. Rocklin, M.D.
M. Ballow, M.D.

Objectives: To determine the efficacy of transfer factor treatment in patients with cellular immunodeficiency.

Technical Approach: See original protocol

Progress and Results: Since inception, this protocol has provided the treatment basis for four individuals with T cell immunodeficiency disease. These individuals suffered recurrent candida and chronic mycobacterial infections. Three individuals failed to improve; one had a prolonged remission. All have been reported previously. No patients were studied in FY 78. The protocol has also provided funds for resident teaching in the area of reconstitution of immunodeficient individuals.

Conclusions: Therapeutic indications for transfer factor have been considerably clarified in the past two years. No indications were met in the past year. The protocol should therefore be terminated.

Funds Utilized, FY-78: None

Funding Requirements, FY-79: None

Publications: Whitcomb, M.E. and Rocklin, R.E.; Transfer Factor Therapy in a Patient with Progressive Pulmonary Tuberculosis. Ann. Int. Med. 79:161, 1973.

Type of Report: Final

Work Unit No.: 3103

Title of Project: Techniques for the Detection of Antinuclear Antibodies.
Comparative Study.

Principal Investigators: Oliver J. Lawless, LTC, MC
Bernard H. Berne, MD, PhD.

Objectives:

(1) To compare immunological techniques currently available for the detection of antinuclear antibodies (ANA) in patients with rheumatic disease processes.

(2) To assess such techniques as regards:

(a) Sensitivity
(b) Specificity especially as regards differentiation of systemic lupus erythematosus (SLE) from rheumatoid arthritis (RA), scleroderma, polymyositis, juvenile rheumatoid arthritis, mixed connective tissue disease (MCTD), gout and degenerative joint disease.

(3) To ascertain the association between positive tests and clinical activity of disease.

(4) To assess the reproducibility of positive tests and their quantitation.

(5) To ascertain the association, if any, between levels of ANA determined by the radioactive DNA binding test (Farr technique), and other methods, such as counterimmunoelectrophoresis (CIEP).

(6) To analyze the cost and usefulness of the various methods of ANA detection.

Technical Approach: Frozen sera from a panel of 300 patients of the Rheumatology and Clinical Immunology outpatient department were used after thawing. The sera were drawn from patients with active and inactive SLE, RA, other connective tissue diseases, gout and degenerative diseases. Many of these sera were collected from the same patients at different stages of their illnesses for the purpose of performing longitudinal studies. All sera were obtained for diagnostic purposes.

Sera were randomly assigned a number and tested blindly in duplicate. The major techniques investigated were fluorescent antinuclear antibodies (FANA) with mouse liver and KB cells, antibodies to DNA by complement fixation, antibodies to DNP by complement fixation, binding of 3-H and 125-I DNA by sera, using the Farr technique, and measurement of antibodies to DNA by the FIAX immunofluorescence technique, the Lederle Latex LE Test and counterimmunoelectrophoresis (CIEP). Where appropriate, several

different antigen preparations were tested to establish the most precise and specific methods for diagnosing the diseases under study.

Results: In early studies, six techniques were used to detect the incidence of antinuclear antibodies in Systemic Lupus Erythematosus (SLE) and connective tissue diseases, to compare the sensitivity and specificity of these techniques. The techniques used were — 1) Indirect Immunofluorescent assay using fluorescein conjugated antihuman IgG on two substrates: (a) Mouse liver sections — FANA-ML, (b) KB tissue culture cell line — FANA-KB. 2) Complement Fixation tests for (a) Anti-DNA antibody, and (b) Anti-DNP antibody. 3) DNA binding assay by Farr technique using 14-C labelled KB DNA. 4) Latex agglutination LE slide test (Lederle).

One hundred serum samples were assayed by all six techniques from patients with the following diagnosis: - 24 patients with ARA criteria for SLE; 35 with Classic RA; 5 with Juvenile RA; 6 with Progressive Systemic Sclerosis (PSS); 4 with Polymyositis (PM); and 26 controls. Positive results were interpreted as follows: FANA-ML = 1/20; FANA-KB = 1/640; DNA/DNP Comp. Fix. titers = 1; DNA binding = 40%; Latex LE = Percent, positive results are listed in the following Table:

TEST	CONTROLS	SLE	RA	JRA	PSS	PM
FANA-ML	4%	100%	31%	0%	35%	0%
FANA-KB	0	100	34	25	100	50
CFIX. DNA	0	17	0	0	0	0
DNP	0	25	6	20	0	0
DNA Binding	0	38	0	0	0	0
LATEX LE	0	20	9	0	0	0

Nine of 24 patients with + FANA tests displayed peripheral patterns of nuclear fluorescence. All 9 (100%) had abnormal DNA binding results, and either nephritis or systemic vasculitis. The FANA-KB test was found to be exquisitely sensitive yielding titers = 5,120 in SLE and PSS patients, and patterns more easily distinguishable than the FANA-ML. This increased sensitivity was however accompanied by a reduced specificity for the diagnosis of SLE. While the FANA test with mouse liver and human KB cells detected 100% of SLE patients, they also proved positive in other diseases. The DNA binding test, performed as a Farr technique with 14-C labelled KB-DNA, proved most specific for SLE.

Following our studies the mouse liver FANA was adopted by the main clinical laboratory as a screening test in the rheumatic diseases. We then turned our attention to DNA binding assay and by the Farr technique performed over 1500 of these in patients with SLE and related diseases.

Our first studies with the Farr technique utilized 14-C DNA from human KB cells as the antigen. DNA binding tests were performed on 485 positive FANA patients.

Sera from 73 (15%) were positive with a binding level of 34%, +2 standard deviations above the mean of normal controls. Forty-four (44) of these patients had 3 or more tests performed in a serial fashion at 2 to 2 monthly intervals. Duration of follow-up was variable from a few months to up to 3 years. Frequency of follow-up varied between weekly to 3 monthly intervals. Analysis of data revealed the following results:

(1) 18/44 (40%) of patients with a positive DNA binding test at time of presentation did not have clinical evidence of nephritis determined by active urinary sediment, proteinuria of 600mg/24 hours, or impaired creatinine clearance.

(2) Three patients with SLE and with positive DNA binding tests had clinical and serological criteria for mixed connective tissue disease.

(3) Twenty-three (53%) of patients with positive DNA binding tests had clinical evidence of nephritis, 17 of which were confirmed by biopsy.

(4) 9/10 patients initially treated with aspirin and hydroxy-chloroquine compounds failed to show any change of DNA binding results within two months of treatment.

(5) Thirty-two (72%) were placed on steroids for clinical control of symptoms. In all but 4 of these, the DNA binding results fell within 1 month of commencing steroids, and this was associated with reduction in clinical symptoms. In 2 patients, however, there was either no change in DNA binding or symptoms (both patients were found not taking their medications). In 1 patient, the DNA binding rose after commencing steroids and failed to normalize as did symptoms in response to steroids and azathioprine, one patient had an initial fall in DNA binding and improvement in symptoms, followed by a plateau of DNA binding above normal values and continued symptomatology. Both were unresponsive to increasing doses of prednisone and addition of cyclophosphamide.

Ten patients (22%) showed a relapse in clinical activity while undergoing reduction of steroid dose. In all patients the DNA binding tests were elevated again after an initial fall, and in retrospect could have predicted a return of clinical symptoms.

In general, a positive DNA binding test may be present in patients without clinical evidence of nephritis; it is frequently positive when the disease is active clinically; non-steroidal anti-inflammatory agents do not alter DNA binding results; a reduction followed by a rise in the test results may predict a flare in clinical activity of the disease.

In 1976, the manufacturer of the 14-C DNA discontinued sales of this product because of production difficulties. We then proceed to test 125-I labelled DNA preparations from KB cells. We found that 125-I assays were simpler to perform than those based on 14-C, since they involve a gamma radiation emitter rather than a beta emitter, and thus do not require the use of scintillation fluid and transfer of precipitates from the reaction

tubes. However, since 125-I has a relatively short half life (60 days) compared to 14-C, the DNA deteriorates rapidly. Thus, the same 125-I labelled DNA preparation cannot be used over a prolonged period of time. We found that different 125-I DNA preparations obtained from the same manufacturer often precipitated differently from each other when tested under identical conditions with the same patient's serum. Some DNA preparations therefore produced a larger percentage of binding with a given serum than other did. This impeded standardization of the assay. We minimized this variable by choosing a standard positive serum (from a lyophilized batch obtained from an acute SLE patient) which was used as a standard in all assays. A system of units was developed referable to this standard, and all unknowns were compared to it. By thus eliminating dependence on the actual percentage of DNA bound using different preparations, inter-assay variability was reduced.

Using the 125-I DNA binding assay with DNA from human KB cells during a 12 month period, we found that we could readily differentiate patients with acute SLE from controls and from those with little active disease in most cases in a study of 96 patients with SLE and related diseases. In 27 of these, serial studies were performed on at least three samples taken at different stages of the disease. Invariably, the highest levels occurred when the disease was most active. In several cases, we were able to predict a clinical exacerbation a month before it became evident by the presence of a high or a rising level of DNA binding. In all cases, DNA bindings fell as the disease remitted. However, some cases (60%) showed decreases to within the normal range when the disease was in relative remission, while others (40%) maintained levels which were lower than their highest ones but were still significantly above the normal range. The patients with persistent elevations had no system involvement such as nephritis which could differentiate them from those whose levels fell to within the normal range. Prolonged follow-up will be necessary to determine whether those patients with persistently high DNA bindings have prognoses that are worse than those whose levels normalized.

A study of synthetic DNA's was begun using tritiated double stranded deoxyadenylic-thymidylic acid (DAT). This antigen has been reported to be more completely double-stranded than DNA isolated from natural sources. It may thus detect a different spectrum of diseases and be more specific for some forms of SLE (especially SLE with nephritis) than natural DNA preparations. A study of 18 sera from 10 SLE patients showed that the tritiated DAT assay differentiated fewer SLE patients from normals than did the DNA binding assay. A large group will need to be studied to determine whether those with DAT binding elevations share a common system involvement that is different from those with normal bindings.

A study was performed to determine whether counterimmunoelectrophoresis (CIEP) could be adequately used in the management of SLE. In CIEP, only precipitating antibodies to DNA are detected, while all antibodies are measured in the DNA binding assay. A panel of 102 sera from 38 patients with SLE and related diseases was compared using calf thymus DNA in the CIEP assay and 14-C labelled DNA from KB cells in the DNA binding (Farr) assay.

The results are charted below:

DNA Binding	CIEP % Negative	CIEP % Positive
Above 60%	3	32
40-60%	23	26
20-40%	33	21
0-20%	41	21
	<u>100%</u>	<u>100%</u>

(40% is the upper limit of the normal range of DNA bindings)

The Farr technique is the most commonly used assay for detecting anti-DNA antibodies in SLE and related diseases. The FIAx immunofluorescence assay recently developed by IDT, Santa Clara, CA, may provide a rapid and technically simpler alternative to this.

We compared a Farr assay using a 3-H human KB cell dsDNA, with the FIAx method, which utilizes calf thymus dsDNA immobilized on an immunoabsorbant stick and fluorescein-tagged anti-human immunoglobulin. Twelve SLE sera were tested in replicates of 2 or more by both techniques, giving the following within-run precisions:

Serum	FIAx (Index Units)				FARR (% DNA Binding)			
	n*	Mean	SD	CV	n*	Mean	SD	CV
A	6	7.7	0.5	7.3%	6	87%	1.5	1.7%
B	2	3.4	0.4	10.5%	6	53%	6.4	11.9%
C	2	2.0	0.9	47.1%	6	9%	0.8	8.7%
11 x 2**		3.9	0.7	22.0%		50%	2.7	14.1%

*n = number of replicates; ** 11 x 2 = averages of means, SDs and CVs of 11 samples tested in duplicate in a single run, with levels ranging from 2.0 to 6.6 with FIAx and 1.4% to 87%, with Farr.

In a comparison of 12 samples tested on three days in duplicate, the following representative between-run precisions were obtained:

Serum	FIAx			FARR		
	Mean	SD	CV	Mean	SD	CV
A	7.0	0.9	13.1%	86%	1.2	1.4%
D	4.4	1.0	14.1%	62%	6.9	11.2%
E	2.8	0.4	12.4%	21%	10.8	51.1%

Levels in 12 sera tested in both assays showed a strong correlation ($r = 0.861$, $p < 0.001$). Neither assay produced excellent reproducibility.

The Farr technique gave better within-run and between-run precisions at most levels. The FIAX assay required a smaller working time (3 vs 7 hrs) and a reduced time to obtain results (3 vs 30 hrs). The results suggest that it may become a cost-effective alternative to the Farr assay that can avoid the use of radioisotopes, if its precision can be improved.

The FIAX assay appears to be preferable to the Farr assay in that it is faster and simpler. However, the poor reproducibility that we obtained with the FIAX assay demonstrates that problems remain with this technique. We presented the results of our study at the 30th Annual Meeting of the American Association of Clinical Chemistry. Because of the poor precision that we and others found, the manufacturer withdrew the product from the market.

The manufacturer recently revised the FIAX kit and has chosen our laboratory for clinical trials of the new assay prior to marketing. We plan to test this in the near future to extend our comparison.

Our most recent studies with the Farr assay used a ³-H DNA preparation treated with endonuclease to reduce the single strandedness of the preparation. The new preparation is thus more specific for double-stranded DNA than were our previous ones. We have tested this preparation on over 300 SLE sera from patients seen on this service on a routine basis. Results are similar to those found with earlier preparations, but are more reproducible. If the reproducibility of the assay can be maintained over a long period of time, we plan to teach the technique to personnel in the main clinical laboratory of WRAMC and transfer routine testing to that service.

Conclusions:

- (1) FANA tests (mouse liver or KB cell) are the most sensitive tests for the diagnosis of SLE.
- (2) FANA tests should be mandatory in all clinical laboratories supporting a clinical population of connective tissue diseases.
- (3) Introduction of any FANA test needs to be standardized against a defined clinical population of connective tissue diseases, or against a serological panel of defined clinical connective tissue disease subsets.
- (4) The KB FANA test provides a standardized tissue system commercially available, which obviates a need for an animal facility normally essential in providing fresh mouse/rat liver slices.
- (5) The KB system provides more readily visible ANA patterns, which may offer additional antigen specificities over the mouse liver technique, and may have increased clinical significance accordingly. (In our investigations, an increased incidence of KB positivity over mouse liver positivity in Scleroderma, Polymyositis and JRA was found. Since our study, a series of newer nuclear antigens have been defined by other techniques such as PM-1 in Polymyositis (Wolfe et al), Sc-1 in Scleroderma, (Alarcon-Segovia et al), and SS-A, B, C, three new antigens in Sjogren's Syndrome (Alspaugh and Tan). This observation will be further amplified

in a future research protocol).

(6) A positive FANA test is therefore mandatory for the diagnosis of SLE.

(7) Negative FANA tests on repeated testing virtually excludes the diagnosis of SLE from the clinical standpoint. (There are a small number of exceptions to this, however, probably in less than 1% of cases).

(8) A positive FANA, however, may mean other connective tissue disease or drug induced ANA.

(9) A double stranded DNA test when tested by RIA is specific for the diagnosis of SLE, and should be available for separating Lupus from other CTD and drug-induced positive ANAs.

(10) Routine commercially available DNA preparations from reputable companies do not contain fully double stranded preparations (eg. Searle, Electronucleonics, and others) and reagents need to be available to define the % double strandedness in the preparations. Furthermore, there is lot-to-lot variation in double strandedness of each preparation.

(11) Specificity of reagents can be tested either by using enzyme - endonuclease treatment or defined antibodies with monospecificity of reaction.

(12) These latter points (10 and 11) significantly impeded our research effort. They need to be widely disseminated within the MHSS and the Rheumatology community.,

(13) Our method of solving this reagent problem has been to have a reagent prepared in frozen aliquots, namely dsDNA of KB type that is endonuclease treated and usable over a prolonged period, i.e., 5 years, in order to provide reproducibility of test results against appropriate controls.

(14) CIEP technique and comp. fix. dsDNA techniques have relevance in the clinical setting only when RIA assay is not available. Because of reduced sensitivity relative to RIA their application should be limited to laboratories who do not have RIA capability. Because of their specificity over FANA in diagnosis of SLE versus other CTD, they do have limited application. Quality control of the DNA preparations is however critical as mentioned above in regard to RIA assay.

(15) Currently, FANA mouse liver assay is available at clinical pathology, WRAMC, while dsDNA RIA is available in our laboratory. New projects will be submitted to apply the latter test to clinical therapeutic studies regarding affinity testing of anti-ANA antibodies in SLE.

(16) Any new tests such as Crithidia or FIAX immunoabsorbance assay should be standardized against both FANA, dsDNA RIA, and a clinically defined population of connective tissue disease patients.

(17) Many of these observations have been presented, and several publications are currently in preparation.

(18) The availability of a well-defined clinical population of patients, and a serological bank of antisera with defined specificities is a unique attribute of our service for providing training to fellows in clinical immunology and immunopathology.

(19) Consideration should be given to development of an Army-wide system for standardization of diagnostic reagents pertaining to the diagnosis of connective tissue diseases.

(20) Such a system would have major significance in the quality of patient care throughout the MHSS, and would be a major advance in the national attack on arthritis.

(21) Currently no such standard system is available in the country.

Funds Utilized (FY 78)

Personnel: One GS-9, Step 8, Civilian Technician \$6,206.00
(2/5 time).

Supplies: 6,000.00

Publications:

Lawless, OJ and Whelton, JC: Comparison of techniques and use of KB cell lines for the detection of antinuclear antibodies. Proceedings, VIth Pan American Congress on Rheumatic Diseases. June, 1974.

Berne, BH, Terrell, R, Snyder, K, Zimmerman, DH and Lawless OJ: Antigen related discrepancies in DNA binding activities in systemic lupus erythematosus (SLE) as measured by counterimmunoelectrophoresis (CIEP) and ammonium sulfate precipitation (ASP). Program, Southeastern Regional Meeting of the American Rheumatism Association, Atlanta, GA. December 1977.

Berne, BH, Lawless, OJ: Clq reactive immune complexes in Sjogren's syndrome. Proceedings of the XXVIth Colloquium, Protides of the Biological Fluids, Brussels, Belgium. May 1978.

Berne, BH, Snyder, K, and Lawless OJ: Comparison of anti-DNA antibody levels detected by the Farr technique and the FIAX immunofluorescence assay. Program, 30th Annual Meeting, American Association for Clinical Chemistry, San Francisco. July 1978. (Clinical Chemistry 24:1018, 1978).

Type of Report: Terminated.

Date Prepared: 29 September 1978.

Work Unit No.: 3105

Title of Project: An Evaluation of Immunologic Response in Ragweed-Sensitive Patients by New Techniques.

Principal Investigator: Richard Evans, COL MC
Chief, Allergy-Immunology Service

Objectives: To study the effects of high dose specific immunotherapy on allergic rhinitis and extrinsic asthma. The goal has been to document in an objective manner any change in sensitivity to an offending antigen subsequent to allergy injection therapy.

Technical Approach: All participants entered into this study in the past year had allergen induced bronchospasm. A detailed history and physical examination was performed. Patients were selected because of relatively severe specific aero-allergen induced asthma. An assessment of each individual's degree of sensitivity to the offending antigen was performed as follows:

In vivo tests:

- a) Serial skin test titration
- b) Antigen bronchial challenge

In vitro tests:

- a) Leukocyte histamine release (LHR)
- b) Total serum IgE
- c) RAST (specific IgE) - when technically possible.

After the above baseline studies, high dose specific immunotherapy is begun. The patients are followed clinically with repeat of all the above studies at six month intervals.

Progress & Results: In the first phase of this study, twenty-two patients with ragweed allergic rhinitis were studied. The results were published in the Journal of Clinical Investigation as cited in previous annual progress reports.

In 1977 and 1978 twelve patients with allergen induced asthma were studied in a similar manner, with the addition of bronchoprovocation testing. The results in the circumstance of bakers asthma have also been presented to the Pulmonary-Allergy Symposium, Fitzsimons Army Medical Center, 8-11 September 1975.

The responses in allergic asthma to specific immunotherapy were highly variable and inconsistent.

6
Conclusions: No conclusive statements regarding immunologic changes can be made from the data collected in asthmatic patients. This is most probably a consequence of the multiple factors (most of which are not immunologic) playing role in the pathogenesis of the disease. It is the opinion of the investigators that this protocol should be terminated.

Funds Utilized, FY-78: \$7,545.00

Funding Requirements, FY-79: None

Publication: Wilbur, R.D. and Ward Jr., G.W.: Immunologic Studies in a Case of Baker's Asthma. J. Allergy Clin. Immunol. 58:3, 1976.

Type of Report: Final

Work Unit No.: 3109

Title Of Project: Complement Deficiencies and their Relationship to Diseases in Man

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associate: Richard Evans III, COL MC

Objective: The complement system, a series of interacting proteins, plays an integral role in the inflammatory response. It is clear that an intact complement system is indispensable in the defense against infections. In other instances activation of the complement system, with generation of phlogistic mediators, may have detrimental consequences for the host. This ongoing project investigated not only the integrity of the complement system in patients with recurrent infection but also the active participation of this system in various disease states.

Technical Approach: Our laboratory has the capability of measuring C₃, C₄, and C₃ activators. These complement components are determined by radioimmunodiffusion.

Progress and Results: We have continued to screen a number of patients presenting with recurrent infections. We identified a boy whose only immunologic abnormality was a markedly diminished C₄. Clarification of this defect was important since C₄ deficiency in man and experimental animals is not associated with recurrent infections. We have identified a 60 year old lady with C₄ deficiency associated with a lupus-like syndrome, (Her C₃ is normal). We do not believe that the C₄ has been consumed as part of a disease related immune process. Rather, we think that absent C₄ in this patient may represent a true congenital deficiency.

We also identified a patient with hereditary angioedema. In the past this disease was often attended by a fatal outcome. Danazol, an impeded androgen, has recently been shown to provide prophylaxis against recurrent episodes. On danazol, our patient is doing extremely well.

Conclusions: Our laboratory has continued to provide useful and necessary information in the management of an heterogeneous group of diseases. Also patients identified as having complement abnormalities provide valuable teaching devices for our fellows and housestaff.

Funding Requirements, FY-78: None

Type of Report: Final

Publication: Selective IgA Deficiency and P;Z Deficiency Associated with Recurrent Sinopulmonary Infections, Emphysema, and Bronchiectasis. Casterline, Charlotte. L., and Richard Evans, COL MC, (Has been accepted in CHEST, in press).

Work Unit No.: 3111

Title of Project: Quantitative Serum IgE in Human Infections, Immune Deficiency States and Diseases with Impaired Cellular Immunity.

Investigators:

Principal: Richard Evans III, COL MC

Associate: Laurie J. Smith, MD

Objectives: To study the role of IgE responses in atopic and nonatopic states with emphasis on a possible association between elevated or decreased levels of serum IgE and allergic disease states, infections, immune deficiency states, and impaired cellular immune responses.

Technical Approach: Serum samples from a patient population described above are collected. These are then analyzed for IgE content using a direct radioimmunoassay. The mean IgE levels in normal adult sera within our laboratory with this assay is 20 I.U./ml with a S.D. of 43 I.U./ml.

Progress & Results: In the past year we have tested 1104 sera for total IgE. Patients studied have included hypersensitivity lung diseases, insect sting allergy, immune deficiency (primary and acquired), idiopathic eosinophilia, and occupational asthma.

The Principal Investigator is chairman of a new committee of the American Academy of Allergy established to evaluate the current status of standardization of in vitro tests in allergy. The first test evaluated was quantitation of total IgE by radioimmunoassay. This laboratory was one of twelve medical center facilities in the U.S. who cooperated in this study. Lyophilized known sera were studied in replicate on the same day and on separate days. These laboratories tested the unknown samples using their own method and a separate kit method. In a similar manner, unknown samples were sent to ten commercial laboratories in the U.S.A. for measurement of variance in the quantitation of total serum IgE by these laboratories. The results were as follows:

Variance in IgE Tests

Laboratory	True Value	Range	Confidence Limits of	Coefficient of Variation
Research	IU/ml	IU/ml	IU/ml	%
own method	200	135-473	60-340	35
kit method	200	133-330	89-311	28
Commercial				
own method	200	130-530	58-342	36
own method	500	130-640	293-707	21

The variance found was considered excessive. In an approach to resolution of this problem, this laboratory is cooperating in the collection and testing of a reference IgE standard. The samples will be lyophilized by the Bureau of Biologics, F.D.A. and distribution to cooperating research laboratories will be by the NIAID, NIH. The true value of the standard will be determined by the cooperating laboratories of which this laboratory is a member.

Finally, a new more sensitive method utilizing a double antibody technique is under investigation. Successful establishment of this method will lower the sensitivity of the test to program quantities. This will enable the quantitation of in vitro synthesis of IgE by human lymphocytes.

Conclusions: This has been a productive protocol resulting in a number of presentations cited in previous progress reports as well as the one below. The protocol should now be terminated on 1 May 1979. The more sensitive assay can be supported after that date by Work Unit No. " " with Dr. Donna Schuster as Principal Investigator. Total serum IgE measurement for patient diagnosis can be obtained through the Clinical Pathology Service or the Allergy teaching service.

Funds Utilized, FY-78: \$7,000.00

Funding Requirements, FY-79: None

Presentation: Variance in the Quantitation of Total Serum IgE in Research and Commercial Laboratories. Committee on Standardization of In Vitro Tests, Richard Evans III, M.D., Chairman. Presented to the American Academy of Allergy, Phoenix, Arizona, March 1978.

Type of Report: Terminated

Work Unit No.: 3113

Title of Project: Synovial Fluid in Rheumatic Disease

Investigators:

Principal: Oliver J. Lawless, MD, COL, MC

Associate: John A. Boice, CDR, MC, USN

Objective: Patients with rheumatic diseases often present joint effusions as part of their symptom complex. Classically synovial analysis has differentiated these into four categories:

- 1) Non-inflammatory fluid characterized by a low white blood cell count and good mucin clot, as exemplified by degenerative joint disease (DJD).
- 2) An inflammatory fluid with elevated white blood cell count and poor mucin clot as found in rheumatoid arthritis (RA).
- 3) A crystal-associated fluid found with gout and pseudogout.
- 4) A turbid fluid with extreme white blood cell count, mucin clot poor, and low glucose, characteristic of infection.

As can be seen by the accompanying tabulated results, these categories are broad and allow considerable overlapping. Nonetheless, the differential diagnosis can be narrowed significantly in most cases, and in trauma, crystal-induced arthritis and infection, it can often be established. This study, therefore will be of aid in the current diagnosis and management of patients seen in the Rheumatology and Clinical Immunology Service and other services in WRAMC.

Technical Approach: At the time of aspiration, synovial fluid is collected in appropriate containers for the determination of clarity, color, viscosity, mucin clot, total white blood cell count, differential cell count, protein, albumin, gamma globulin, glucose, complement (C3, C4, CH50), inclusions, crystals, culture and gram stain. A portion of the sample is stored for future analysis. As results are obtained, a formal assessment is made of the sample and whether they are consistent with the diagnosis. An appendix shows an example of the work sheet used.

Progress and Results: Synovial analysis has been carried out on several hundred samples from a variety of causes of arthritis. These data have been correlated and are summarized in Table 1 insert.

Correlation of these findings with longitudinal clinical studies of the course of the individual diseases will await assignment of new fellow to complete this part of the study and will be on a separate or new protocol.

Conclusions:

(1) No single test, such as the total white blood cell count, can be used to establish a definitive diagnosis of any type of arthritis.

(2) The combination of tests used in this study may likewise not establish the cause of arthritis. However, the combination of tests used enables the number of differential diagnoses to be reduced to a few. The laboratory findings can invariably establish a clinical diagnosis of a definitive nature when they are considered together with the clinical findings.

(3) A total white blood cell count above 50,000, while typical of septic arthritis, can be present in other diseases, e.g., crystal-induced synovitis, JRA, RA and Reiter's Syndrome. This finding mandates the use of a polarizing microscope, appropriate cultures and other tests to avoid inappropriate treatment.

(4) Serologies and complement levels, while having a low incidence of positivity and while never completely diagnostic, may produce important clues to the consideration of connective tissue diseases that may be considered pertinent on clinical grounds alone.

(5) Inclusions, as seen in leukocytes by light microscopy, are significantly more abundant in RA than in other conditions.

(6) A larger number of fluid analyses are required in several categories in order to produce statistically relevant comparisons.

Type of Report: Terminated

Date of Report: 25 April 1979

TABLE I Page 1a

SYNOVIAL FLUID

Minimum Average Maximum	Clarity		Viscosity		Color	Mucin clot		W.B.C. (1x10 ³)	Polymorpho Lymphocytes		Crystals		Total Proteins gm %
	1+ clear 2+ cloudy 3+ " 4+ turbid	1+ good 2+ " 3+ " 4+ poor	1+ good 2+ fair 3+ poor	G F P		%	G P		Gout Pseudo- gout				
Normal Class I	1+ 98%	(33) 1+ 91%	(11) yellow	(36) 94%	(38) 0.013	(37) 11/85	(57) 0%	(19) 1.1					
	2+ 2%	2+ 6%		3% 3%	0.455	88/100	0%	2.4					
	3+ 0	3+ 0%			6.7		(+)	4.8					
	4+ 0	4+ 3%											
Trauma	1+ 69%	(16) 1+ 12%	(16) yellow 87%	(17) 59%	(16) 0.001	(15) 0/01	(17) 0%	(9) 2.5					
	2+ 19%	2+ 13%	red 13%	35%	1.65	48/56	0%	3.58					
	3+ 0%	3+ 31%		6%	5.2	99/100	(+)	5.1					
	4+ 12%	4+ 44%											
Degenerative Joint Disease	1+ 67%	(53) 1+ 64%	(17) yellow	(67) 72%	(65) 0.007	(57) 0/0	(55) 0%	(35) 1.5					
	2+ 23%	2+ 7.5		21%	2.43	30/67	(+)	3.2					
	3+ 6%	3+ 11%		7%	22.8	95/100		5.7					
Systemic Lupus Erythematosus	1+ 26%	(16) 1+ 25%	(8) yellow	(14) 28%	(17) 0.033	(15) 0/0	(18) 0%	(9) 2.3					
	2+ 33%	2+ 12%		28%	8.88	47/54	(+)	4.1					
	3+ 26%	3+ 12%		44%	32.0	99/100		6.8					
Crystal Induced	1+ 21%	(14) 1+ 31%	(16) yellow	(14) 7%	(12) 0.255	(12) 0/0	(15) G 100%	(8) 3.1					
	2+ 57%	2+ 31%		36%	10.78	70/30	P 0%	4.1					
	3+ 14%	3+ 15%		57%	42.3	98/100		4.9					

TABLE I Page 1b

SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C2	C4	CH50	Inclusions (%)
Normal Class I	(6) 45 54 60	(6) 14 20 35	(5) 72 86 98	(50) 0% (+)	(50) 0% (+)	10 (4) 46 70	(0) - (7)	(1) - 70 -	(7) 0% (+)
Trauma	(5) 52 59 63	(5) 12 15 21	(11) 40 95 162	(8) 12.5% (+)	(8) 0% (+)	20 (5) 59 91	(0) - (12)	(3) 30 150 153	(12) 0% (+)
Degenerative Joint Disease	(7) 41 58 64	(4) 9.9 21 33	(37) 63 96 163	(44) 0% (-)	(44) 2% (+)	21 (34) 73 45	(0) - (17)	(10) 30 79 196	(17) 5.8% (+)
Systemic Lupus Erythematosus	(2) 44 54 66	(2) 13 30 47	(7) 37 84 116	(11) 64% (+)	(12) 25% (+)	03 (11) 57 104	(1) - 7.8 -	(3) 30 59 73	0% (+)
Crystal Induced	(3) 60 62 67	(8) 11 17 21	(8) 84 98 118	(7) 0% (+)	(9) 0% (+)	56 (6) 80 104	(0) - (2)	(2) 60 90 120	0% (+)

TABLE I Page 2a

SYNOVIAL FLUID

Minimum Average Maximum	Clarity				Viscosity	Color	Mucin clot			W.B.C. ($\times 10^3$)	Polymorpho Lymphocytes %	Crystals		Total Proteins gm %
	1+	2+	3+	4+			G	F	P			G	P	
Rheumatic Fever	0				0	0	0			0	0	0		0
Rheumatoid Arthritis	1+	10%	(79)	(77)	1+	7%	G	16%	(75)	0.05	0/0	0%	(77)	2.9
	2+	40%			2+	10%	F	17%		11.52	69/31			5.05
	3+	25%			3+	18%	P	67%		36.0	100/100	(+)		7.6
	4+	25%			4+	61%								
Juvenile Rheumatoid Arthritis	1+	9%	(23)	(20)	1+	10%	G	11%	(18)	4.6	0/0	0%	(19)	3.4
	2+	39%			2+	0	F	33%		26.8	73/30			4.6
	3+	30%			3+	15%	P	56%		74.6	95/100	(+)		6.0
	4+	22%			4+	75%								
Ankylosing Spondylitis	1+	0	(1)	(1)	1+	0	G	0	(1)	-	1	(1)	(1)	-
	2+	100%			2+	100%	F	0		4.7	68/21	0%		3.6
	3+	0			3+	0	P	100%		-	1	(+)		-
	4+	0			4+	0								
Sjögrens	1+	0	(2)	(4)	1+	75%			(3)	1.45	14/10	(5)	(4)	4.2
	2+	100%			2+	25%	P	100%		5.35	48/44	25%		5.0
	3+	0			3+	0				13.2	90/86	(+)		6.6
	4+	0			4+	0								
Colitic Arthritis	1+	0	(2)	(2)	1+	50%				4.45	1	(2)	(1)	-
	2+	0			2+	50%	P	100%		13.27	90/0	0%		9.4
	3+	0			3+	0				22.0	1	(+)		-
	4+	100%			4+	0								

TABLE I Page 2b

SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C3	C4	CH50	Inclusions (%)
Rheumatic Fever	0	0	0	0	0	0	0	0	0
Rheumatoid Arthritis	(13) 41 51 57	(13) 18 22 35	(46) 36 87.7 132	(58) 14% (+)	(58) 43% (+)	(52) 10 58.8 148	(1) - 28 -	(4) 30 30 30	(26) 36% (+)
Juvenile Rheumatoid Arthritis	(3) 49 66 93	(1) - 20 -	(16) 51 87 110	(19) 16% (+)	(20) 15% (+)	(20) 50 97 150	(0) - -	(3) 40 100 140	1% (+)
Ankylosing Spondylitis	(1) - 54 -	(1) - 16 -	(1) - 77 -	(1) 0% (+)	(1) 0% (+)	(1) - 115 -	(0) - -	(0) - -	(1) 0% (+)
Gout	(0) - -	(0) - -	(2) 66 84 102	(5) 20% (+)	(4) 0% (+)	(4) 47 64 87	- - -	- - -	-
Cellulitic Arthritis	(0) - -	(0) - -	(1) - 114 -	(2) 0% (+)	(2) 0% (+)	(1) - 37 -	(0) - - -	(0) - -	(2) 0% (+)

TABLE I Page 3a

SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C3	C4	CH50	Inclusions (%)
Reiter's Syndrome	(4) 51 53 62	(4) 18 21 25	(12) 60 88 106	(13) 0% (+)	(14) 0% (+)	83 110 193 (12)	(6) - - -	(6) 120 132 150	0% (+)
Infectious Arthritis	(1) 46%	(1) 21%	(3) 6 76 125	(3) 0% (+)	(3) 0% (+)	74 82.5 91 (2)	(0) - - -	(0) - - -	(1) 0% (+)
Chondromalacia	(0) -	(0) -	(2) 83 89 96	(4) 0% (+)	(5) 0% (+)	- 62 - (1)	0 (1)	(1) - 120 -	(3) 0% (+)
Tuberculosis Arthritis	-	-	-	-	-	-	-	-	-
Gonococcal Arthritis	(0) -	(0) -	(4) 6 11 40	0% (+)	0% (+)	(0) -	(0) -	(0) -	(4) 0% (+)

Work Unit No.: 3117

Title of Project: Evaluation and Study of Patients with Primary and Secondary Immunodeficiency Diseases

Principal Investigators: Arnold I. Levinson, M.D.
Richard D. deShazo, MAJ MC

Objective: To study patients with recurrent infection for evidence of immunodeficiency using new laboratory techniques.

Technical Approach: Over the past year this protocol provided the laboratory resources for study of over 20 patients referred for evaluation of immune deficiency from both the pediatric and medical services at Walter Reed Army Medical Center as well as from other medical facilities. The workups included evaluation of both humoral and cellular immunity as well as neutrophil function and included the following:

1. Humoral Immunity
 - (a) Quantitative immunoglobulins determined by radial immunodiffusion
 - (b) B cell rosettes (EAC's) using sheep RBC's, rabbit anti sheep IgM and mouse C5 deficient sera as source of complement
 - (c) Surface immunoglobulins on B cells utilizing (F(ab')₂) fragment goat antihuman polyvalent-immunoglobulin (IgG, IgM, IgA)
2. Cellular Immunity
 - (a) Skin reactivity was evaluated with the use of intradermal skin tests with SKSD, mumps, trichophyton, candida and PPD.
 - (b) DNCB sensitization and rechallenge
 - (c) Mitogen as well as specific antigen proliferative studies involving cell cultures of patients lymphocytes with Con A, PHA, SKSD and candida.
 - (d) Mixed lymphocyte cultures were done with allogenic cells.
 - (e) T cell rosettes (E rosette) were determined with the use of sheep RBC's.
3. Complement components (C₃, C₄) were also determined utilizing radial immunodiffusion techniques.
4. Neutrophil function was evaluated through the use of Rebeck skin windows, chemiluminescence and chemotaxis.

Progress & Results: To date eleven of the above patients evaluated have been found to have aberrant immune function. These include one patient with partial DiGeorge Syndrome, two patients with common variable hypogammaglobulinemia, one with hyper IgE syndrome, four IgA deficiency patients as well as two patients with probable congenital complement deficiencies.

Conclusion: This protocol has provided for a broad based immunologic laboratory approach to the evaluation of patients with primary and secondary immunodeficiency diseases. Several of the techniques have recently become more standard and less investigative. This protocol should now be terminated. A subsequent appropriately more specific follow-up to this study has been submitted and approved.

Funds Utilized, FY-78: \$6,175.00

Funding Requirements, FY-79: None

Publications: Millunchick, E., Levinson, A.I., deShazo, R. and Ruymann, F.: Coexistent Congenital Agammaglobulinemia and Chromosomal Aberration. Submitted J. of Peds.

Presentations: 1. Regulatory Defects in Immune Deficiencies by Dr. Levinson at Children's Hospital, September 1978.
2. Aspects of Immune Deficiency in Man by Dr. Levinson at Washington Hospital Center Seminar, February 1978.
3. Lymphocyte Subpopulations - Seminar - Levinson and Fauci - American Academy of Allergy, March, 1978.

Type of Report: Final

Work Unit No.: 3123

Title of Project: Study Immune Mechanisms in Systemic Lupus Erythematosus

Investigators:

Principal: Oliver J. Lawless, Colonel, MC

Associate: Bernard H. Berne, PhD, MD

Objective: To simultaneously assess the function of the phagocytic T & B components of the immune system in the production of the symptoms of acute Lupus, and to compare these findings with those found during inactivity or remission of the disease.

Technical Approach: Lupus is an antigen induced disease, the major responsible antigen being double stranded DNA. The modulation of phagocytic, T & B cell function by antigen, antibody, and antigen antibody complex has pertinence not only to Lupus but to all infectious diseases where antigen persistence plays a role, but also to the mechanisms of transplantation, and tumour rejection. Lupus patients are unique in that the DNA antigen, and antibody systems can be isolated, purified, and tested in an vitro system on the cells of the patient without potential injury to him. Identification of the modulation mechanism in Lupus would have direct importance to host resistance to infection, and to transplant and tumour rejection, all of which are major thrusts of military research.

Inflammation in Systemic Lupus is caused by immune complexes. Patients with acute disease frequently have local deposition of complexes, high levels of free DNA, anti DNA, and elevated anti DNA levels after treatment of serum with anti DNase. They also have elevated levels of proteins and immunoglobulins, reduced levels of complement C3, C4, and CH50 and depressed T cell function. Rheumatoid factors are frequently found also. It is our hypothesis that complexes are deposited because of ineffective clearance by the phagocytic system. The mechanism for clearance of these complexes has not been directly defined in Systemic Lupus Erythematosus. It is our proposal to study the role of DNA ag, anti DNA antibody, and DNA-anti DNA complexes and rheumatoid factor on phagocytic, T & B cell function in acute active, and inactive Systemic Lupus Erythematosus (SLE). Immune complexes incite an inflammatory reaction at the site of their deposition eg. kidney, skin, lung, etc. Clearance of complexes from the circulation is by the RE system - monocytes and polys, of peripheral blood, and by fixed and wandering RE cells of parenchymal organs eg. liver, kidney, etc.

Phagocytic clearance has not been measured in SLE. All assays for functional activity of phagocytes depend upon indirect assays such as NBT test, iodine incorporation into protein and clearance studies using radio labelled macro-aggregated proteins. Clearance of DNA anti DNA complexes with radioactively labelled DNA would provide us with information more specifically relatable to phagocytic function in this disease.

T lymphocyte number and function have been shown to be reduced in acute untreated SLE. The mechanism responsible for this has not been defined. Three potential explanations for this phenomenon can be proposed (1) the presence of lymphocytotoxic factors, (2) the presence of blocking factors that are not cytotoxic, (3) the presence of immune complexes that "alter" lymphocyte re-activity, (4) the presence of antibody against T cell receptors in SLE sera. Fundamental to the understanding of blocking or enhancing factors on the T lymphocyte is definition of the role of complexes of DNA anti-DNA made up in antigen excess, equivalence and antibody excess, on these cells as we have shown that depending upon the Ag-Ab ratio of these complexes serum containing these complexes can be either enhancing or blocking to Ag and PHA induced T cell responses.

HLA profiles have been recently linked with a high statistical significance to certain diseases considered to be immunologically induced. HLA profiles in SLE have been reported to yield variable results. It is to be noted however that SLE serum can display blocking factor activity, in relation to lymphocyte function and HLA expression. Culture and washing of peripheral blood lymphocytes of SLE patients for twenty-four hours may yield additional HLA antigens not detectable at time zero. The relationship of this finding to the presence of DNA-anti DNA complexes needs further definition and confirmation. Antigen, and mitogen induced T cell responses result in lymphocytic blast transformation and lymphokine production in tissue culture. Lymphokines have shown to have specific effects on polys, and monocytes as well as other lymphocytes. If T cell responses are diminished by reason of cytotoxic factors or blocking factors then theoretically mediator release from T cells would be suppressed, and accordingly loss of T effect on poly and monocyte would be expected, a phenomenon that could contribute to decrease in phagocytic function and clearance of complexes.

The practical application of this project is as follows. If one can show that complexes present in serum are responsible for suppression of T cell directly and poly and monocyte indirectly then two potential treatment approaches are virtually free of toxicity. (1) Plasmapheresis for removal of complexes, (2) transfer factor therapy, made from the patient himself during the non-acute and "suppressed" phase of this disease with a view to

(a) removing the blocker, (b) boosting the deficient cell system responsible for defective clearance of complexes.

B2 microglobulin has been shown to be (1) produced by cells including T cells and monocytes in tissue culture, (2) to be metabolized by tubular epithelium cells of the kidney, (3) to be high in the serum of patients with severe renal disease, and (4) high in the urine of patients following transplantation. It has furthermore been shown to be similar to the C3 domain on the H chain of IgG molecule and to be closely linked to the HLA antigen bound on the surface membrane of T lymphocytes.

It is theoretically possible therefore that serum levels of B₂M will be altered in SLE, and urinary levels may be altered prior to evidence of clinical activity of the disease. Epstein has shown that free light chains in an effort to identify if these measurements afford earlier recognition of exacerbation of SLE. Within this overall project the following individual projects and protocols are proposed:

Phagocytic Function

- (1) Development of in vitro phagocytic assay using C¹⁴ labelled DNA anti DNA complexes of fixed molar ratios and peripheral blood monocytes and polys,
- (2) Measurement of effect of Ag (DNA) Ab (anti DNA) C¹, and Rheumatoid Factor on this assay system,
- (3) Measurement of effect of lymphokines on this assay, from normal, and active and inactive SLE patients lymphocytes,
- (4) Measurement of effect of lymphotoxic serum on this assay.

Lymphocyte T Function

- (1) DH to battery of Ags,
- (2) Enumeration of T & B cell numbers by Rosette and surface staining technique,
- (3) Measurement of T cell response to Ag, MLC, PHA, PWM, DNA and DNA anti DNA complexes, in different molar ratios,
- (4) Measurement of the effect of Ag - Ab complexes in different molar ratios on the kinetics of T cell responses in normal and SLE patients in response to Ag and PHA and PWM,
- (5) Measurement HLA profile of SLE patients and the influence of time, Ag and Ab complex on this profile,

- (6) Measurement of lymphokine production in SLE lymphocytes and the effect on macrophage migration inhibition and leukocyte migration inhibition.

B Cell Function

- (1) Measurement of IgG, A, M, D and E levels,
- (2) Measurement of antinuclear antibodies by FANA, and DNA binding technique,
- (3) Measurement of C3 and CH50 complement levels.

Immune Complexes (IC) Detection

Immune complexes will be detected by a solid phase sandwich radioassay using labelled Clq, a part of the first component of complement. Clq, a protein with a molecular weight of 600,000 can bind and precipitate with IC, although existing tests utilizing this reaction are generally either cumbersome or insensitive, they have been shown to be useful in documenting the rise in IC during exacerbations of SLE.

While several polyanions (DNA, Heparin, Endotoxin, etc.) are known to also bind to Clq, the specificity of the reaction with IC appears sufficient to enable this to form a sensitive assay for IC, as increased binding correlates with disease activity in SLE. Improvements in methodology such as the radioassay proposed here will allow an assessment of the actual effects of non-specific binding on the assay for IC.

Urine Proteins

Measurement of urinary light chain excretion, and B₂ microglobulin excretion in the urines of quiescent and active Lupus patients.

Progress and Results:

T Cell Function

We previously identified on this protocol that lymphocytes of acute SLE patients are functionally depressed in response to the antigen SKSD and PHA and ConA, and further that this suppression was increased by the presence of acute SLE plasma compared to control plasma. We now have attempted to characterize the nature of this lymphocyte suppression by further characterization of SLE acute plasma.

A fundamental question exists as to whether the impaired lymphocyte responsiveness in SLE patients is due to an intrinsic deficiency at the T cell level or to an acquired defect in T cells due to circulating humoral factors present during the acute phase of this disease. In an attempt to answer this question, sera was taken from 9 SLE patients and were characterized in regard to the following parameters: 1) FANA positivity; 2) DNA binding %; 3) DNA binding capacity; 4) C3; 5) C4; 6) Clq; 7) CIC (that is circulating immune complexes as measured by Clq binding assay for CIC). Lymphocytes were taken from a normal donor whose responsiveness to SKSD, PHA, ConA, PWM were evaluated in the presence of normal serum versus 9 SLE sera both in the presence and absence of 1 and 10 ug of DNA added to each culture. All cultures were set up in quadruplicate and the means and standard deviation calculated. Statistical analysis was by Student T test. An antigen binding capacity of 10 ug/ml was chosen to divide the SLE sera into high and low binders. The results show as in Table 1 that for the 9 SLE sera only the SKSD responses were significantly suppressed below the control serum levels. However, all responses were suppressed when tested against the high binder group sera. Added DNA caused further suppression.

TABLE I.

	Control Serum			SLE Group (9)			High Binders (4)		
	Mean	CPM	SD	Mean	CPM	P	Mean	CPM	P
<u>SKSD</u>	6,339	+	495	2,501	.001		1,691	.001	
1 ug DNA	7,269	+	240	2,381	.001		1,448	.001	
10 ug DNA	1,858	+	77	955	.001		628	.001	
<u>PHA</u>	29,997	+	2,368	24,597	NS		20,595	.1	
1 ug DNA	27,916	+	1,273	22,454	NS		10,067	.025	
10 ug DNA	25,789	+	1,061	17,825	NS		11,481	.001	
<u>Con.</u>	19,824	+	267	14,389	NS		12,162	.01	
1 ug DNA	21,241	+	791	13,591	.05		9,111	.001	
10 ug DNA	15,111	+	430	8,731	.05		4,863	.001	
<u>PWM</u>	15,079	+	579	14,414	NS		10,880	NS	
1 ug DNA	17,548	+	265	12,494	NS		8,341	.01	
10 ug DNA	9,168	+	315	8,228	NS		4,716	.01	

None of the SLE sera were cytotoxic for a panel of lymphocytes using both rabbit and human complement. These data suggest an extrinsic mechanism for lymphocyte suppression in SLE. These sera were further studied for cytotoxicity against the control cells in the presence of rabbit complement, guinea pig complement, and normal human serum as a source of human complement using the Terasaki assay for cytotoxicity. No cytotoxicity was found using the guinea pig or normal human serum complement. Thus the suppression activity of the SLE serum can not be considered to be on the basis of cytotoxic antibodies. In an attempt to ask the question as to whether these 9 sera altered the E Rosette cells of the lymphocyte donor used in the lymphocyte transformation study the following experiment was set up.

Control lymphocytes were isolated from the same donor washed by 4 times and then incubated either with the autologous normal control serum or 9 different lupus sera, and followed by four further washings prior to performing an E Rosetting procedure. The results were that the total E Rosettes of the normal control lymphocytes in the presence of normal serum was 67%. The mean number of E rosettes in the presence of the 9 different SLE serums yielded results of 57% total E Rosettes. Thus there was a 10% reduction in the number of total E Rosettes following incubation of normal cells with the SLE sera. Thus in summary serum from active SLE patients can cause suppression of SKSD, PHA, ConA, LT of normal cells, but fail to suppress pokeweed mitogen PWM stimulation. Suppression is increased by the addition of added DNA. This suppression does not appear to be on the basis of lymphocytotoxic antibody. The SLE sera have the ability to suppress the total number of E Rosettes that is T cells-as well as to functionally impair these cells. Our results suggest that all of the abnormalities defined to be present in acute SLE cells can be induced in normal lymphocytes by acute SLE sera. The data suggest indirectly that this suppression of number and function of T cells maybe related to immune complexes of DNA anti DNA. However, other interpretations are possible particularly in relation to lymphocytotoxic antibody. Further studies are in progress in an attempt to clearly define the nature of the serum suppressing factor and will be the subject of a pending separate protocol on evaluation of the role of DNA anti DNA complexes on lymphocyte transformation.

Immune Complexes in SLE, Sjogren's Syndrome and other rheumatic diseases.

As part of this project, we developed an assay for immune complexes (IC) using the precipitation of Clq (the first component of complement) in the presence of polyethylene glycol (PEG). In this assay, Clq is labelled with 125-I and reacted with IC, which binds to it. The complex of IC and Clq precipitates upon addition of 2.5% PEG.

The mixture is then centrifuged and the supernatant is removed. The amount of 125-I that is measurable in the precipitate reflects the quantity of IC originally added.

We found only traces of IC in 38 of 40 normal sera tested. Elevated amounts were present in two, perhaps because of concurrent disease or artifacts induced by freezing and thawing. (We found that we could only obtain reliable results when we froze and thawed serum only once).

Marked elevations occurred in some, but not all, SLE patients. In general, there was a correlation with disease activity (especially with renal disease). In some instances, Clq binding activities correlate better with clinical activity than did measurements of

anti-DNA antibody levels. In others, however, Clq binding tended to remain elevated after clinical remission occurred. The relation of DNA binding and Clq binding in SLE remains unclear.

Elevated Clq levels were found in other autoimmune disorders. In rheumatoid arthritis, levels were often very high, and correlated well with rheumatoid factor (RF) levels. In a study of 10 patients, the highest RF levels occurred in patients with high apparent IC levels. Since RF is often found complexed as IC, such a finding is not surprising, although it is at variance with some reports in the literature using similar IC assays. These studies showed a poor correlation between IC and RF levels, and suggest that our assay may be performed in a better manner.

We also found IC elevations in post-renal transplant patients and in chronic active hepatitis. In Sjogren's Syndrome (SS) an autoimmune disease characterized by the sicca syndrome of dry eyes and dry mouth, we found frequent increases in Clq binding.

Of the 18 SS patients tested, 10 had the sicca complex alone (SC), 5 were associated with rheumatoid arthritis (RA) and 3 with mixed connective tissue disease (MCTD). The sera of 42 apparently normal blood donors and laboratory personnel were used as controls. Nine patients with RA and 19 with systemic lupus erythematosus (SLE) were also studied.

All sera were checked for rheumatoid factor (RF) and fluorescent antinuclear antibody (FANA) positivity. We defined positive sera in the Clq assay as those having a percentage of Clq precipitated that was greater than 2 standard deviations above the mean of at least 10 "normal" controls tested simultaneously.

The results showed that 12/18 (67%) of SS patients had positive tests for IC compared with 2/42 (5%) of "normal" controls. In SLE, 63% were positive, as were 77% in RA. IC levels correlated closely with RF levels as determined by bentonite flocculation in RA.

Of those patients with SC alone, 5/10 (50%) had a positive IC test compared with 4/5 (80%) with both SS and RA and 3/3 (100%) with SS and MCTD. Of the 10 SC patients 4 had a positive RF and one had a positive FANA. Two of the 10 patients with SC alone had negative RF tests; one of these was FANA positive and both were IC positive.

These data show that circulating immune complexes are commonly found in SS patients and can be detected in the absence of RF, suggesting a possible role for immune complexes other than RF in this disease. However, when RF is present in patients with RA or SS or both, IC levels correlate closely with those of RF. It is therefore probable that RF is a major contributor to IC levels detected by the Clq binding assay when it is present.

Studies on IC in SLE and Sjogren's syndrome continue in progress. Clarification of the antigens and antibodies involved in IC formation remains an important goal in this area, as does the definition of the association of clinical parameters and IC levels. Since several different IC assays are used by different investigators, there are few extensive published studies using any single test. Thus, many of our studies represent original investigations and lead to new avenues of research in this area.

Type of Report: Terminal

Work Unit No.: 3138

Title of Project: Immunologic Mechanisms of Cutaneous Reactions to
Inhalant Antigens

Principal Investigators:

Richard D. deShazo, M.D.

Objectives: To determine the pathophysiologic mechanism of delayed in
time dermal reactions to antigen as a model for similar reaction in
other allergic disease.

Technical Approach: See original protocol and 1978 addendum.

Progress & Results: We have determined that these reactions are IgE
dependent and histamine independent. They result from activation of the
coagulation system by IgE dependent mechanisms. This is a new and
previously unreported finding.

Conclusions: A partial explanation for the pathophysiology of these
reactions has been discovered.

Funds Utilized, FY-1978: \$1380.0

Funding Requirements, FY-1978:

Personnel - Presently available

Equipment - Presently available

Supplies - \$1000.00

Stipends for patients: \$1000.00

Consultant and processing of tissue: \$1200.00

Travel: \$ 600.00
Total \$3800.00

Publications: The Late Cutaneous Reaction J. Allergy Clin. Immunol
61: 186-187, 1978.
The Late Cutaneous Reaction. J. Immunol (In Press)

Type of Report: Interim

Work Unit No.: 3139

Title of Project: Immunologic Function of Human Tonsil and Adenoid Cells

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associates: Michael Johns, MAJ MC
Carol Marcks, MS

Objective: This study was designed to investigate, in comparative fashion, immunologic function of human tonsil, adenoid, and blood lymphocytes.

Technical Approach: The technical approach has previously been described in detail in our original protocol.

Progress and Results: In the first phase of this study, lymphoid populations in the tonsil and adenoids were determined. In contrast to the blood, tonsils and adenoids are primarily B-cell organs. We next examined the proliferative responses of tonsil, adenoid and blood lymphocytes. In general, all three tissues responded to the same peak doses of the mitogens Concanavalin A (Con A) and Phytohemagglutinin (PHA). Similar responses were noted to the antigen, Candida. In contrast, the peak response to the antigen, SKSD, occurred at a lower concentration in both tonsil and adenoid tissue than the peripheral blood lymphocytes.

Kinetic studies indicate that the peak response to PHA occurs later in tonsil and adenoid cells than blood (5 days versus 3 days). The peak response to Con A occurs at the same time in all three tissues (3 days).

Conclusions: These preliminary studies have provided information on the lymphoid constituents of tonsils and adenoid tissue. Functional assessment indicates that mitogen and antigen reactive cells are present, although the kinetics of their response differ from that of blood lymphocytes. It is likely that this difference is due to the smaller number of T-cells in the tonsils and adenoids. Future studies on purified populations of T-cells from tonsil, adenoid and blood will investigate this possibility. Lymphocytes reactive to SKSD, an antigenic determinant of the streptococcal organism, were found in tonsil and adenoid tissue. Thus, patients with recurrent tonsillitis have cells reactive to the specific infecting organism at the focus of infection as well as in their peripheral blood.

Funding Requirements, FY-78: None

Publications: In progress

Type of Report: Final

Work Unit No.: 3140

Title of Project: Hyposensitization: Long Term Sequelae

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associates: Richard Summers, LTC MC
Mark Stein, LTC MC
Richard Evans, CCL MC

Objective: This study was undertaken to determine if long-term hyposensitization causes late sequelae, particularly those reflecting aberrant immunologic responses.

Technical Approach: Atopic individuals receiving five or more years of hyposensitization with allergenic extracts were selected for this study. Atopic volunteers not on hyposensitization served as controls. The following studies were performed using standard techniques: quantitative immunoglobulins, rheumatoid factor by latex fixation, Coombs' test, fluorescentantinuclear factor, C₃ and C₄, cryoglobulins, and E and EAC rosettes, and the Clq precipitation assay for circulating immune complexes.

Progress and Results: This study was completed in 41 patients on long term hyposensitization therapy and 22 control volunteers. The study was extended for one more year in FY-78 and the E and EAC rosettes and the Clq precipitin assays were completed.

The treatment and control groups were comparable in age, sex and duration of atopic illness. There was no sign or symptom of lymphoproliferative or immune complex disorder. There were no significant differences between the study and control groups on SMA-12, hematologic or urinalysis testing. There were no significant differences between groups in any of the tests mentioned above.

Conclusion: Atopic individuals receiving five or more years of hyposensitization with allergenic extracts showed no increased autoimmune, collagen vascular, or lymphoproliferative disease. In addition, chronic hyposensitization did not have adverse effects on immunologic reactivity as assessed by a number of immune parameters. Particularly noteworthy was the absence of immune complexes in the serum of patients undergoing long-term hyposensitization. This study represents the first systematic investigation of potential adverse effects of long-term hyposensitization.

Funds Utilized, FY-78: \$10,005.00

Funding Requirements, FY-79: None

Publications: Levinson, A.I., Summers, R.J., Lawley, T.J., Evans III, R.,
and Frank, M.M.: Evaluation of the adverse effects of long-
term hyposensitization. J. Allergy Clin. Immunol.
62:109, 1978.

Type of Report: Final

Work Unit No: 3141

Title: A Multiclinic Long Term Comparative Efficacy and Safety Study of Albuterol Versus Isoproterenol Nebulizer Solution (by Hand-Bulb Nebulization) in the Treatment of Reversible Obstructive Airway Disease in Adults.

Investigators:

Principal: Richard W. Huss, M.D., MAJ, MC
Associate: Richard Evans, M.D., COL, MC
Richard Summers, M.D., LTC, MC

Objectives: 1. To determine the efficacy, safety and tolerance of albuterol nebulizer solution when administered by hand-bulb nebulization for six months in patients with reversible airway disease. Clinical efficacy and safety will be monitored.
2. To determine the spectrum and frequency of side effects which may be associated with chronic treatment with albuterol nebulizer solution delivered by hand-bulb nebulization.
3. To determine whether the magnitude and duration of bronchodilation is maintained when albuterol nebulizer solution delivered by hand-bulb nebulization is used regularly for six months.
4. To compare the effects of albuterol with those of isoproterenol nebulizer solution.

Technical Approach: the patient comes to the clinic in the morning having taken none of his medications. He then administers ten inhalations of the drug (either albuterol or isoproterenol). Observations are made over the next six hours to include heart rate and blood pressure and pulmonary function tests. A lead II rhythm strip is obtained and chest auscultation is periodically done.

Progress and Results: this study was terminated 29 Sep 1977 and Clinical Investigation Committee was so advised. 14 patients participated in the study. There were no reports of any adverse effects of the drugs on any of the patients. Albuterol was found to be a significantly better bronchodilator in terms of airway response and duration of effect than isoproterenol.

Conclusions: in this study albuterol was found to be a significantly better bronchodilator than isoproterenol.

Publications: none. An abstract of this paper was presented in September 1978 to the Annual Meeting of Military Allergists in Denver, Colorado. This is to be published in the proceedings of that meeting.

Type of Report: terminated.

Work Unit No.: 3143

Title of Project: Biologic (Skin Testing) Potency of Allergenic Extract Reference Preparations.

Investigators: Richard Evans, COL MC
Harold Baer, Ph.D.

Objectives: To establish a biologic potency for comparison with in vitro potency testing of four different allergenic extracts, prepared by the FDA, Bureau of Biologics, and intended for use as US reference standards.

Technical Approach: Allergenic extracts of short ragweed, Timothy grass, white oak tree and birch tree, prepared and lyophilized by FDA, are resuspended in buffer diluted and used for serial titration skin testing in allergic volunteers. In addition, whole blood is drawn from the volunteers and tested for in vitro antigen induced leukocyte histamine release and serum specific IgE antibody by the RAST procedure.

Progress and Results: Serial titration skin testing with these extracts has been performed as follows:
48 ragweed pollen sensitive patients
45 Timothy grass pollen sensitive patients
9 oak pollen sensitive patients
12 birch pollen sensitive patients
This data has provided for a biologic potency characterized of these extracts which are to be used as F.D.A. reference standards. In addition, these standards have been used as a basis for comparison of commercially prepared extracts. This testing was performed by iso-electric focusing, leukocyte histamine release and indirect RAST assay.

Conclusions: This project is now completed. The results have and will continue to contribute significant information toward providing a means for standardization of allergenic extracts.

Presentations:
Abstract #165 EVALUATION OF POLLEN EXTRACTS USING ISO-ELECTRIC FOCUSING. Martha C. Anderson, M.S., Harold Baer, Ph. D., and Richard Evans, M.D., American Academy of Allergy, Phoenix, Arizona, March 1978.

Workshop "Standardization of Allergenic Extracts,"
conducted by Richard Evans, M.D., American Academy of
Allergy, Phoenix, Arizona, March 1978.

Presentation by Richard Evans, M.D. to Pulmonary-
Allergy Symposium, Denver, Colorado, September 1977.

Type of Report: Terminated.

Work Unit No.: 3144

Title of Project: Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma

Investigators:

Principal: Richard Evans III, COL MC

Associates: Laurie Smith, M.D.
Richard Summers, LTC MC

Objectives: To characterize a group of atopic asthmatics by their alpha and beta adrenergic as well as cholinergic responses, looking in particular for a cholinergic imbalance.

Technical Approach: All patients will have extensive initial allergy workup including skin testing to inhalant allergens and an antigen bronchial challenge. The following tests will be performed at NIH:

- 1) Oral aspirin challenge
- 2) Eccrine sweat responses to saline mecholyl and propranolol
- 3) Cutaneous blood flow by means of Xenon disappearance from an injected site
- 4) Pupillometry to measure pupil responses to Carbachol and Phenylephrine
- 5) Response of cyclic nucleotides to intravenous injections of very low doses of isuprel

The following tests will be performed at WRAMC Allergy Clinic:

- 1) Mecholyl bronchial challenge with air and He/O₂
- 2) Histamine bronchial challenge with air and He/O₂

Note: Certain equipment must be expanded and modified.

Progress & Results: During the previous year we studied 16 mild allergic asthmatic patients with methacholine bronchial challenges, eccrine sweat responses to methacholine, cutaneous blood flow responses to phenylephrine injections, pupillometry responses to carbachol and phenylephrine and IV injection of small incremented doses of isoproterenol.

In addition 7 normal controls were studied with all of the above tests and a total of 31 normal controls received some combination of the above tests but not all.

A new finding is that asthmatics show consistently more sensitivity in threshold response to alpha adrenergic agents than normal controls. Further analysis of the data shows an inverse relationship between beta adrenergic sensitivity and cholinergic sensitivity as measured by methacholine challenge, and a direct relationship between alpha adrenergic sensitivity and cholinergic sensitivity in asthmatic patients.

Conclusions:

1) Asthmatics demonstrate an array of autonomic nervous system abnormalities which separate them as a group from the nonasthmatic population. These abnormalities include:

Beta adrenergic unresponsiveness
Alpha adrenergic hyperresponsiveness
Cholinergic hyperresponsiveness

2) As a group the degree of cholinergic hyperresponsiveness is inversely related to the degree of beta adrenergic responsiveness.

3) The degree of cholinergic hyperresponsiveness is directly related to the degree of alpha adrenergic responsiveness.

4) An additional item of equipment, Collins spirometry microprocessor is needed to achieve the necessary accuracy for helium-oxygen spirometry measurements of small airway function.

5) This project merits high priority for continued funding.

Funds Utilized, FY-78: \$500.00

Funding Requirements, FY-79:

<u>Personnel:</u>	None		
<u>Equipment:</u>	Microprocessor for Collins spirometer		\$2500.00
<u>Supplies:</u>	Mouthpieces	\$100.00	
	Methacholine	250.00	
	Graph Paper	200.00	
	Other consumables	450.00	1000.00
<u>Travel:</u>			600.00
<u>Other:</u>	Reprints and publication costs		750.00
			<u>\$4850.00</u>

Publications:

1) Abstract: Alpha and beta adrenergic responses in asthma. J. H. Shelhamer, D. D. Metcalfe, L. J. Smith, R. Evans, D. Reingold, M. Kaliner, Am. Rev. Resp. Dis. 117, 80, 1978.

2) Alpha adrenergic hyperresponsiveness in asthma:
Analysis of vascular and pupillary responses. NEJM, in
press.

3) An abstract "The Array of autonomic abnormalities
in Bronchial Asthma" has been accepted for presentation
by Dr. Smith to the American Academy of Allergy, March
1979.

Type of Report: Interim

Work Unit No.: 3145

Title of Project: A Fluorescent Test for Extractable Nuclear Antigen

Investigators:

Principal: Paul A. Wehrle, CPT, MC

Associate: Oliver J. Lawless, COL, MC

Objectives: To establish a rapid reliable fluorescent assay for the diagnosis of mixed connective tissue disease.

Medical Application: At present the diagnosis of mixed connective tissue disease (MCTD) necessitates serologic confirmation by a hemagglutination test for extractable nuclear antigen (ENA). This test is difficult to perform due to the need to extract pure ENA from crude calf thymus tissue. A fluorescent test will avoid the need for calf thymus tissue. KB cells, another source of ENA, moreover, can be purchased commercially and stored frozen until needed. The availability of a fluorescent assay would make this diagnostic test readily available to all facilities instead of only the few centers which now perform the hemagglutination test.

Status: Mixed Connective Tissue Disease is characterized clinically by features of systemic lupus erythematosus, scleroderma, and polymyositis. Renal involvement is minimal and steroid response is usually excellent. It is characterized serologically by high titered, speckled patterned fluorescent antinuclear antibody (FANA), a hemagglutinating antibody to ENA, and a low incidence of antibody to native deoxyribonucleic acid (DNA). The ENA has shown previously to consist of two separate components. A ribonucleoprotein (RNP) which is sensitive to ribonuclease (RN-ase) digestion; and a second, resistant to RN-ase, which has identity with the SM antigen commonly found in Systemic Lupus Erythematosus (SLE).

Plan: We propose to perform the FANA test utilizing KB cells on the sera of all clinic patients which have a positive FANA in a speckled pattern by the standard mouse liver method. These will be from patients with SLE, scleroderma, and MCTD. After treatment with RN-ase, the test will be repeated to determine the change in titer when compared with pre-treatment assays.

- (A) PATIENT SELECTION: Patients will be selected who exhibit the clinical characteristics of MCTD as defined by Sharp.
- (B) CONTROLS: Sera will be obtained from the following groups:
- 1) Normals: No evidence of a connective tissue disease.
 - 2) SLE Patients: a) Those with positive FANA in speckled pattern.
b) Those with FANA in other (solid, rim, nucleolar, cytoplasmic) pattern.
 - 3) Patients with speckled pattern FANA and a connective tissue disease other than MCTD, i.e., Scleroderma, Sjogren's.

Progress and Results: This test was run on 10 controls, 24 MCTD patients, 14 SLE, 3 Scleroderma and 1 Rheumatoid Arthritis. Results of the control studies are as follows: 10/10 were positive by the KB cell test; the serum was undiluted; 2/10 were positive by the 1:10 dilution; 1/10 was positive at a 1:20 dilution. Positive tests there were defined at a titer of 1:40 or greater by the KB fluorescent cell test.

Following KB cell treatment with either 4 or 30 mg% of RNase, all control tests became negative. All control sera were likewise negative by the mouse liver technique of fluorescent antinuclear antibody testing.

RNase Digestion of KB cells

In a preliminary experiment, a positive KB FANA at a titer of 1:20,480 was reduced to 1:640 following 4 mg% of RNase treatment. This was further reduced to a titer of 1:20 following usage of 30 mg% of RNase. The concentration of RNase used for the remainder of the experiment was 30 mg%.

MCTD Results

Of the 24 MCTD patients run on a FANA by the mouse liver technique 20/24 revealed a speckled pattern. Tested by the KB FANA all 24 had positive speckled patterns. The mean titer of the 24 positive MCTD sera was 1:11,820 with a range from 1:20 to 1:40,960. Following RNase treatment of the KB cell both by 4 and 30 mg% RNase all 24 reduced. In 13/24 tests 30 mg% RNase treatment reduced the titer of positivity below that reached by treatment with 4 mg%. Eight were unchanged, while 3 caused an increased titer by a single dilution which was probably not significant. Mean titer of the entire group following treatment with 30 mg of RNase was reduced from a mean pre-RNase titer of 1:11,820 to a post-RNase titer of 1:1,000. The range varied from 0 staining to a maximum titer of 1:2,560. The results of the total ENA, RNP and SM run by Dr. Sharp's laboratory were as follows:

All of the 24 samples tested yielded a positive ENA test by a hemagglutination technique, measurement of SM antibody was negative in 8 of these samples while RNP was present in all. In 5 of these 8 Sm negative samples RNase treatment totally eliminated a positive KB FANA, while in 3 the positive FANA was not totally eliminated, however reductions were marked from 1:10,240 to 1:320 in 2 samples, and a reduction from 1:20,000 to 1:640 in one sample. In the remaining 16, complete elimination of the positive KB test was not possible. We plan to retest those 3 patients sera who showed discordance between the absence of Sm and total elimination of the KB FANA by increasing the percentage of RNase or the duration of treatment and retesting them to investigate if total elimination can take place.

Summary and Conclusions: RNase treatment of the KB cell FANA appears to be a promising method to detect ENA and specifically the RNP fraction of ENA. Currently Sm and RNP tests are detected by immunodiffusion and hemagglutination. Availability of a single fluorescent antibody test that provides titers, patterns, including elimination of the speckled pattern as a method for detecting RNP would make this latter test available to clinical laboratories with fluorescent microscopic capabilities and would thus expand the clinical definition of those patients with mixed connective tissue disease.

Funding: We wish to request continued funding of this project for the following reasons:

- 1) To increase the numbers of those MCTD patients with Sm negativity.
- 2) We currently have a contract with Dr. Sharp to perform ENA and Sm on patients with MCTD.
- 3) We will thus be able to further correlate our results with Dr. Sharps measuring ENA, RNP, Sm.

Funding Requirements:

Personnel:

Equipment: None

Supplies: (Consumable) \$750.00
KB Cell Slides

Publications: 500.00

Travel: 500.00

Type of Report: Interim

Work Unit No.: 3146

Title of Project: Immunotherapy Kit Potency Persistence

Investigators:

Principal: Richard J. Summers, M.D. LTC MC

Associates: Richard Evans III, M.D. COL MC
Terry V. Guilbert, MAJ MSC

Objective: The study is designed to determine the persistence of biological potency of allergy extracts during shipment and use.

Technical Approach: RAST (Radioallergosorbent Test) will be performed to determine potency persistence.

Progress & Results: The extracts have been shipped and returned. Aliquots are being taken at intervals and final results should be available in four months.

Conclusions: No conclusions can be made until all results are in.

Funds Utilized, FY-78: \$500 of estimated total cost of protocol

Funding Requirements, FY-79:

Personnel: One GS-7 technician, currently employed, 2 weeks/year

Equipment: No new equipment is required

Supplies: Consumable - needles, syringes and
RAST testing \$3700.00

Travel: None

Total \$3700.00

Publications: None

Type of Report: Interim

Work Unit No.: 3147

Title of Project: Hymenoptera Venom Safety and Efficacy Evaluation as Allergen Immunotherapy in Insect Sting Allergic Patients

Investigators:

Principal: Daniel A. Ramirez, MAJ MC

Associate: Richard Evans III, COL MC

Objective: To establish the safety and effectiveness of hymenoptera venom preparations in the prevention of anaphylactic reactions following hymenoptera stings.

Technical Approach: Patients with a history of having systemic reactions following a hymenoptera sting are evaluated by skin testing using a skin test titration technique from 10^{-3} ug/ml up to 1 ug/ml. Concordant venom RAST titers are also obtained. Routine chemistries, CBC with sedimentation rate, urinalysis, C3, C4, FANA, and venom specific titers of IgE and IgG will be followed every 3 months.

Progress & Results: A total of 75 patients have been evaluated by skin testing for inclusion into the study. The lyophilized reagents used were as follows:

1. Honey Bee Venom Lot No. DA 2358
2. Polistes Wasp Venom Lot No. DD 6555
3. Yellow Hornet Venom Lot No. DA 4877
4. Yellow Jacket Venom Lot No. DD 6377
5. White Faced Hornet Lot No. DD 6556
6. And also for treatment Mixed Vespid (White Faced Hornet, Yellow Hornet, Yellow Jacket) Lot No. DD 6379

All these allergenic extracts have expiration dates of April 1981 and are manufactured by Pharmacia Laboratories, Division of Pharmacia Inc., Piscataway, New Jersey 08854.

From these 75 patients, 24 have been selected for venom immunotherapy. Nine patients have so far reached a dose of venom of 40 ug or greater. No patients have experienced systemic reactions, though 2 patients have had large local reactions which have required a reduction of their dose. No abnormalities of the laboratory parameters have thus far been detected. The specific IgE and IgG antibody titers will be performed in the spring of 1979 utilizing a radioimmunoassay.

Conclusions: Hymenoptera Venom extracts have so far been shown to be safe in use for immunotherapy. The demonstration of efficacy in preventing anaphylactic reactions in sensitive patients awaits elective sting challenges in the spring of 1979.

Funds Utilized, FY-78: None

Funding Requirements, FY-79:

<u>Supplies:</u>	(syringes, and radioimmunoassay materials)	
	Syringes	\$ 100.00
	Radioisotopes	550.00
	Rabbit antihuman IgE F(c)	1000.00
	Goat antirabbit sera	150.00
	Rabbit antihuman IgG F(c)	900.00
		<u>\$2700.00</u>
<u>Travel:</u>	(presentation at National meeting)	500.00
		<u>\$3200.00</u>

Type of Report: Annual Progress Report, Interim.

Presentation:

1. An abstract for presentation by Dr. Ramirez of part of these data regarding diagnosis has been accepted for the scientific section of the American Academy of Allergy meeting in March 1979.
2. An abstract for presentation by Dr. Evans of part of these data regarding treatment has been accepted for a scientific workshop of the American Academy of Allergy meeting in March 1979.

Work Unit No.: 3148

Title of Project: The histologic evaluation of Diffuse Lung Disease in Sjogren's Syndrome by Transbronchial Lung Biopsy.

Investigators:

Principal: Robert R. Tucker, MAJ, MC
Kenneth Hunt, COL, MC

Associate: Oliver J. Lawless, COL, MC

- Objectives:
- (A) To evaluate the microscopic pulmonary changes found by transbronchial lung biopsy of patients with proven Sjogren's.
 - (B) To evaluate therapeutic response to Sjogren's pulmonary disease to steroids and/or immuno-suppressive agents and to correlate this response with histologic abnormalities.
 - (C) To determine the incidence of Sjogren's Syndrome in a population of patients with idiopathic pulmonary fibrosis by screening patients with diffuse interstitial lung disease with serologic studies, Schirmer's testing, and if appropriate, lip biopsy.

Medical Application: In the past, the diagnosis of pulmonary disease in patients with Sjogren's Syndrome has been made either on the basis of open lung biopsy or on the basis of the clinical and roentgenographic presentation. Evaluation of these patients with the procedures of transbronchial lung biopsy (TBBX) via the fiberoptic bronchoscope has not been reported. This procedure has much less morbidity than the open thoracotomy technique; its drawback, however, is in the small size of specimens provided. Nevertheless, a small specimen provides a more rational basis for therapeutic decision than does no tissue at all. It is anticipated that this study will define the role of TBBX in the diagnosis of Sjogren's pulmonary disease and that it will, in addition, provide a rational basis for therapy. The second aim of this study is to identify any patients presenting with idiopathic pulmonary fibrosis who have Sjogren's Syndrome as its etiology.

Status: Pulmonary manifestations of Sjogren's Syndrome are divided into two main groups: (1) bronchitis sicca, and (2) parenchymal or pleural based disease. After Shearn (1), the latter is comprised of (a) pulmonary infections (bronchitis, pneumonia, bronchiectasis), (b) fibrosing alveolitis, (c) pleurisy with or without effusion, and, (d) nodular parenchymal disease.

Strimlan's recent review of the pulmonary manifestations of Sjogren's Syndrome has shown abnormalities to be present in 9% of cases. They have found no way of differentiating between diffuse interstitial fibrosis, lymphocytic interstitial pneumonitis, and malignant lymphoma by the roentgenographic appearance.

Transbronchial lung biopsy has been described as a safe, accurate technique of arriving at a tissue diagnosis in diffuse lung disease. This technique has been recently introduced, and has not previously been used to assess or follow patients with Sjogren's Syndrome. By making an early histologic diagnosis in cases of Sjogren's Syndrome, it is anticipated that therapy be planned more rationally and that prognosis might be determined more accurately.

Plan: The patients, offered the opportunity of entering this study, will come from two sources. The first group will consist of persons with biopsy proven Sjogren's Syndrome evaluated through the WRAMC Rheumatology Clinic on an inpatient or outpatient basis.

Sjogren's diagnosis will be made on the basis of keratoconjunctivitis, symptoms of xerostomia, and positive sicca. Kerato-conjunctivitis will be defined with Schirmer test, utilizing topical ophthalmic anesthesia, with less than 5 millimeters of wetting interpreted as positive. Evaluation of filamentary keratitis will be evaluated by 1% Rose Bengal staining of the interpalpebral area and further confirmed by slit lamp examination. These tests will be done by the Ophthalmology Department WRAMC. Xerostomic and positive Sicca will be further defined by labial lip biopsy, where minor salivary glands are removed and graded after Greenspan. (Where 0 would be defined as acinary cells free of round cell infiltration, to 4 with the presence of more than one focus of fifty or more round cells per 4mm of section).

Sjogren's will be considered a definite diagnosis with objective evidence of keratoconjunctivitis sicca and changes on lip biopsy. Serologic studies will include rheumatoid factor (latex fixation with Bentonnite flocculation titer), serum protein electrophoresis, quantitative immunoglobulins, FANA, C3, C4, Westergren erythrocyte sedimentation rates, urinalysis, and serum electrolytes. Skin testing for anergy will be conducted by the outpatient Allergy Department, WRAMC, with tests to include, intermediate PPD, and SKSD (1:50), monilia, and mumps.

All those having diffuse pulmonary infiltrates on routine chest x-ray, will be offered the opportunity of participating in this study. All will have pulmonary function testing performed to include pre and post bronchodilator spirometry diffusion, arterial blood gases, flow volume loop, closing volume, airway resistance and conductance determination by plethysmography, static compliance, and exercise testing.

The second group will consist of patients evaluated by the WRAMC Pulmonary Clinic on an inpatient or outpatient basis with the diagnosis of idiopathic pulmonary fibrosis. These patients will undergo an evaluation to include the serologic testing noted above, Schirmer's test, and labial lip and TBBX if indicated.

Progress and Results: This protocol remains active however, to date only 2 patients who fulfilled the study criteria were seen in the clinic during the past year. Both underwent biopsy.

Following biopsy both were placed on corticosteroids. One patient with inflammatory infiltrates showed significant improvement in symptoms and pulmonary function tests following steroid treatment. The other patient failed to improve following steroid treatment. His biopsy revealed fibrosis.

While the above results are interesting, they are too small to draw any conclusions at this time. It is planned to continue this protocol for another year to obtain at least 10-12 patients. Dr. Timmons will be replaced by Dr. R. Tucker. Dr. Torrington will be replaced by Dr. K. Hunt. Dr. Lawless continues as associate investigator on the protocol.

Funding Requirements:

Publication costs

\$500.00

Work Unit No.: 3149

Title of Project: Investigation of Immunologic Imbalance in Atopic Dermatitis

Investigators:

Principal: Donna Lynn Schuster, MAJ MC

Associate: Richard Evans III, COL MC

Consultant: Arnold I. Levinson, MD
University of Pennsylvania, Philadelphia, Pennsylvania

Objective: The purpose of this study is to determine the presence of a possible immunologic imbalance in atopic dermatitis, particularly in regard to suppressor T cell function as well as to study the regulation of IgE in this patient population.

Technical Approach: Two types of assays were used for measuring suppressor cell dysfunction. In the first assay mononuclear cells obtained from the atopic dermatitis patients and from the matched nonatopic control subjects were cultured in vitro with Con A for twenty-four hours. The capacity of these Con A activated cells to suppress the proliferative response of three different homologous cell populations in coculture experiments was determined. In the second assay, mononuclear cells from the same atopic dermatitis patients and control subjects were stimulated with varying doses of mitogen at day 0 and after twenty-four hours of preculture. In this system, increased proliferative response of precultured cells as compared with 0 hour cells has previously been shown in normal subjects to represent loss of suppressor cell function in vitro. The lack of such an increase implies aberrant SC function.

In addition to the above two assays, we are currently using standard rosetting techniques to characterize lymphocyte subpopulations in patients with atopic dermatitis and elevated IgE.

In man, T gamma cells have been shown to suppress differentiation of B lymphocytes. Conversely, T mu may provide helper function. In this group of experiments OXRBC sensitized with either rabbit IgM or rabbit IgG anti-OXRBC are used in a rosetting procedure to identify T mu or T gamma respectively.

In addition to looking at T subpopulations we are also planning to set up a double radioimmunoassay for IgE in order to measure low level IgE supernatants of cocultures of lymphocyte subpopulations in our patient population as well as in control groups. This assay will help us further dissect the regulation of IgE in atopic dermatitis. Reagents for this assay will be obtained from the University of Maine. Although this route is expensive, these reagents are very difficult to manufacture locally. The reagents from the University of Maine are of proven high quality.

Progress & Results: The data from the first assay showed no significant difference in Con A activated suppressor cell function when compared with that of control subjects. In the second assay, twenty-four hour precultured cells of AD patients and control subjects both showed an increased proliferative response to mitogen when compared with respective 0 hour cultures.

To date, our data of T subpopulations in our patient population indicate that the absolute as well as the relative numbers of T gamma cells are markedly reduced whereas the total lymphocytes as well as T mu cells were comparable to the control group.

Conclusions: Suppressor cell function as tested in the first two assays appears normal in AD patients with elevated IgE. It should be emphasized that these assays measured the capacity of AD patients' cells to suppress proliferative responses only. We are planning to look directly at the modulation of IgE itself.

In addition, we have found an imbalance in T cell subpopulations in our patients with atopic dermatitis and elevated IgE. It remains to be determined if this aberration is a marker for the elevated IgE or for the disease state itself.

Funds Utilized, FY-78: \$4380.00

<u>Personnel:</u>	20 hours of GS9 technician time per week x 52 weeks		
<u>Equipment:</u>	Glassware, culture plates, pipettes, plastic tubes, etc.		\$3000.00
<u>Supplies:</u>	Culture media	\$2500.00	
	Radio isotopes	2500.00	
	Reagents for equipment (coulter counter CO2)	2000.00	
	Specific immune antisera and rabbit sera (anti FC, anti IgE FC, anti rabbit IgG)	5000.00	12000.00
<u>Travel:</u>			600.00
			\$15600.00

Publications: Schuster, D.L., Pierson, D., Bongiovanni, B., and
Levinson, A.I.: Suppressor cell function in atopic
dermatitis associated with hyper IgE, J. Allergy Clin.
Immunol. 61:143, 1978 (abst.).

Schuster, D.L., Pierson, D., Bongiovanni, B. and
Levinson, A.I.: Suppressor cell function in atopic
dermatitis associated with elevated IgE, J. Allergy
Clin. Immunol. (in press).

Type of Report: Interim.

Work Unit No.: 3150

Title of Project: Comparison of Two Licensed Commercially Available Short Ragweed Extracts Differing in Their Ability to meet the Bureau of Biologics (BOB) Proposed Criteria of Potency

Investigators:

Principal: Richard Evans, MD, COL MC

Associates: Paul C. Turkeltaub, MD
Harold Baer, PhD
FDA, NIH, Bethesda, MD

Objective: To evaluate the ability of new Bureau of Biologics (FDA) potency standards to identify potent allergenic extracts.

Technical Approach: Patients with ragweed hayfever will be matched and divided into two groups and assigned one of two licensed short ragweed extracts differing in potency according to BOB criteria. The patients will be placed on standard immunotherapy and followed through the ragweed pollen season with daily symptom index scores.

Progress and Results: This protocol is combined protocol with BOB, FDA, HEW, Bethesda, MD, and the NIH. No suitable patient volunteers were found at this medical center in FY-78. One of the investigators, Dr. Turkeltaub, has obtained the necessary patient population for the study at the NIAID, NIH health clinic.

Conclusion: Since no WRAMC patients have been entered into this protocol, the WRAMC approval should be terminated.

Funds Utilized, FY-78: None

Funding Requirements, FY-79: None

Type of Report: Final

Work Unit No.: 3151

Title of Project: Allergic Disease Center Study of Hymenoptera Insect
Venom as an Agent for Diagnosis

Investigators:

Principal: Daniel A. Ramirez, MAJ MC

Associate: Richard Evans III, COL MC

Objective: To establish the effectiveness of hymenoptera venoms as skin
testing agents in making the diagnosis of insect sting allergy

Technical Approach: Patients with a history of allergic reactions to
hymenoptera stings are skin tested with the commercially available whole body extracts and with insect
venoms using a skin test titration of 10^{-3} ug/ml up
to 1 ug/ml. In addition to the comparison between
whole body extract and venom skin testing, the skin
testing will be compared to the venom RAST.

Progress & Results: Patients were skin tested with lyophilized venoms of
Honey Bees, Yellow Jacket, Hornet, White Faced Hornet
and Wasp. These are provided by the NIAID, NIH.
Catalog was A(631→ 635)-902-585, received November
1978.

So far 5 patients have been skin tested with these
agents. 4/5 have had positive skin tests to at least
one of the venoms.

Conclusions: No firm conclusions can be drawn yet.

Funds Utilized, FY-78: None

Funding Requirements, FY-79:

<u>Supplies:</u> (syringes, etc.)	\$300.00
<u>Travel:</u> (presentation of paper)	600.00
	<u>\$900.00</u>

Publications: None

Type of Report: Annual Progress Report, Interim.

Work Unit No.: 3952

Title of Project: Factors Affecting Theophylline-Half-Life

Investigators:

Principal: Paul F. Walker, MAJ MC

Associates: Rodolfo Bongiovanni, 1LT MSC
Richard Evans III, COL MC

Objective: Determine variations of biologic half-life of Theophylline comparing values obtained following intravenous infusion of Theophylline in normal volunteers and asthmatics under various clinical states and treatment programs.

Technical Approach:

A. Population of non-asthmatic "normal" volunteers (6) will be given a single intravenous dose of aminophyllin (5 mg/kg) by rapid infusion (5 min). Blood samples will be obtained immediately prior to the infusion and at 0, 5, 10, 15, 30, 45, 60, 90, 120, 240, 360, 480 minutes following infusion of aminophyllin.

B. A population of known reversible asthmatics (15) will be studied under the conditions stated above in section A. Pulmonary function testing will also be obtained immediately prior to the infusion and at one hour following completion of the infusion, and six hours following completion of the infusion. These asthmatics will be studied under Plan A under the following conditions:

1. Acute onset dyspnea and bronchospasm, not reversible by epinephrine.

a. Aminophylline 5 mg/kg in rapid infusion
Solu-medrol 2 mg/kg IV Push
Bronkosol 0.5 mg/2.5 mg NS by inhalation

b. Blood samples obtained as in Plan A

c. Pulmonary functions obtained as in Section B.

2. Clinically stable, on outpatient theophylline, corticosteroids, either alupent or terbutaline orally

3. Clinically stable on theophylline, corticosteroids

4. Clinically stable on theophylline, terbutaline/alupent.

5. Clinically stable on outpatient theophylline alone.

C. In sections 2-5, patients will be given 5 mg/kg aminophyllin in a rapid intravenous infusion with blood samples and pulmonary function studies obtained as previously described.

Progress & Results: To date: Pharmacokinetic studies have been carried out on six normal volunteers on three separate occasions manifesting no significant difference in clearances, $T_{1/2}$ alpha, and $T_{1/2}$ beta in a given individual from day to day.

A total of 16 pharmacokinetic studies have been performed. Ten patients have been studied. Eight of the ten studied under conditions of acute asthma with follow-up studies obtained under one of the previously-mentioned treatment programs.

In all cases so studied, there is a difference in the rate of clearance and in the $T_{1/2}$ beta of at least two hours; the results found in individuals in acute asthma being shorter than results in these individuals when disease is quiescent.

Pharmacokinetic studies have not been completed for the other categories to date due to limitations determined by difficulties in obtaining optimal control of the disease state, and due to problems with compliance in the case of several of the participants.

Conclusions:

A. There appears to be a significant affect on the clearance and $T_{1/2}$ beta of theophylline that is determined by the activity of the basic disease process.

B. There are indications that clearance and $T_{1/2}$ beta of theophylline may be significantly prolonged by the use either of corticosteroids, beta-stimulating agents, or both.

C. There appears to be no significant difference in the clearance $T_{1/2}$ alpha, and $T_{1/2}$ beta of theophylline in healthy individuals on a day-to-day basis.

D. Study should be continued to further examine and document these preliminary findings and to determine the effect multiple-drug therapy on the biologic clearance and half-life of theophylline.

Funds Utilized, FY-78: \$.00

Funding Requirements, FY-79:

<u>Personnel:</u>	4 hrs/wk technician time		
<u>Supplies:</u>	Syringes	\$ 250.00	
	IV set ups	1500.00	
	Drugs	250.00	
	HPLC C18 columns	750.00	\$2750.00
<u>Travel:</u>			500.00
<u>Other:</u>	Computer time		500.00
			<u>\$3750.00</u>

Publications: None

Type of Report: Interim

Work Unit No.: 3154

Title of Project: Evaluation of prostaglandin producing suppressor cells in cancer patients. WRAMC #7802.

Investigators:

Principal: Richard D. deShazo, MAJ MC

Co Investigators: Archie Brown, MAJ MC
Daniel Kimball, LTC MC
H. Blum, M.D.

Objectives: To determine the presence of these suppressor cells in patients with cancer and explore their response to prostaglandin synthetase inhibitors.

Technical Approval: See original protocol

Progress and Results: This protocol was approved in its final form only recently. Work on it began in August. 5 normal controls have been studies and the methodology for the technique perfected. Patients are now being fed into the study.

Conclusions: None

Funding Requirements: FY-79

Personal - presently available

Equipment - presently available

Supplies - \$7966.0

Travel - \$500.00

Other \$ 300.00 (serum indomethsin levels by commercial laboratory)

Publications - None

Type of Report: Interim

Work Unit No.: 4106

Title of Project: Post-Operative Treatment of Women with Resectable Ovarian Cancer with Radiotherapy Alkeran or No Further Treatment.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Johannes Blom, MD and William Neglia, MAJ, MC

Objectives: To determine the best postoperative approach to treatment of patients with Stage IA and IB ovarian cancer.

Technical Approach: Postoperative patients with ovarian cancer, Stage IA and IB which is totally removed at surgery, will be treated with either radiotherapy, chemotherapy or no further treatment.

Progress & Results: Nineteen patients have been entered from Walter Reed and 168 from the entire GOG. This protocol closed 17 March 1978, and is currently in press for publication.

Conclusions: There is no statistical difference in the response or survival of the three arms.

Funding Requirements: No local funds are required since this protocol is funded through the GOG.

Type of Report: Completed

Work Unit No.: 4113

Title of Project: Cooperative Gynecologic-Oncology Group

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Paul B. Heller, MAJ, MC; Roger Lee, LTC, MC; William Neglia, MAJ, MC;
Jeffrey Weisbaum, MAJ, MC; Johannes Blom, MD

Objectives: The Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, which contains 47 of the major medical centers in the country who are interested in the area of Gynecologic tumor treatment. The GOG is recognized and funded through the National Cancer Institute.

Progress & Results: WRAMC is active in 18 protocols involving treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, and uterine sarcoma. To date, over 700 patients have been registered in this group from WRAMC, and 160 have been placed in specific protocol studies.

Funding Requirements: No local funding is requested as this group is supported by a grant from the National Cancer Institute.

Type of Report: Interim.

Work Unit No.: 4116 Interim Report

Title of Project: The Evaluation of Fetal Systolic Time Intervals and Beat to Beat Interval Variations in Fetal Heart Rate as Early Indicators of Fetal Maturity and Fetal Distress.

Investigator: Henry Klapholz, MAJ, MC

Associate: Frank C. Miller, LTC, MC and Helen Skiba, RN

Objectives: To determine how the systolic time intervals of the fetus may be predictive of early fetal distress in the antepartum and intrapartum period. The establishment of normal values of pre-ejection period and the manner in which it varies with rate, gestational age and conditions of asphyxia will be determined.

Technical Approach:

This will be done by external heart monitoring and doing fetal heart ultrasonography to intergrate these factors on a multiple channel recorder along with maternal heart beat and maternal blood pressure to evaluate the impact of these various factors.

Progress & Results:

Additional patients were studied in whom fetal distress was noted both by abnormal fetal heart rate patterns and Ph below 7.20. Again, the wide normal variance of the PEP was noted and there were differences noted in the asphyxiated vs. the non-asphyxiated group. The normal range of the PED (60-80) was reported in the AFD-ACOG meeting in New Orleans, October 1977.

Conclusions:

This technique does not lead itself to discriminating an asphyxiated from a non-asphyxiated fetus.

Funding Requirements:

None further.

Work Unit No.: 4124 Interim Report

Title of Project: Fetal Intensive Care Monitoring in a Long-Range Continuing Project.

Investigators:

Principal: James Haddock, LTC, MC

Associates: Norman Neches, LTC, MC
Henry Klapholz, M.D.

Objectives: The objective of this research is to evaluate the usefulness of fetal monitoring and labor in detecting early fetal distress and abnormal fetal heart rate patterns. Beginning 1 July 1974 an increased effort was made to monitor all labor (where feasible) utilizing electronic clinical fetal monitoring equipment. A work sheet is completed on each patient and all the FHR tracing are being reviewed. To date the clinical correlations between normal FHR and good 1 & 5 minute Apgar scores has been excellent. Currently work is being done to develop and test a standard code sheet which may be utilized with a computer.

Progress & Results:

(New development) The Hewlett Packard 5600-A OB-GYN Research Computer is being installed. A new protocol has been submitted requesting funding to develop an automated system using our high speed digital computer with analogue to digital converter that will:

1. detect abnormalities of Fetal heart rate
2. quantify them and
3. provide a summary at the completion of the labor.

The criteria of what constitutes fetal distress and an algorithm to optimally summarize such large quantities of data need to be developed.

Funding Requirements:

It is expected that as this project advances a clinical research secretary will be required to collect and process the accumulated data. The services of a computer programmer (FORTRAN) will be required on a half time basis to augment the programming talent in the Department of OB-GYN.

Work Unit No.: 4126

Title of Project: The Clinical Evaluation of a Rapid Method for Presurgical Cleansing of the Hands.

Investigators:

Principal: Frank C. Miller, LTC, MC

Associates: Lawrence Decker, MAJ, MC, John Read, MAJ, MC
Arthur Gross, COL, DC and Duane Cutright, COL, DC

Objectives: To compare the effectiveness of a 90 second pulsed jet hand and forearm wash with a standard 10 minute presurgical scrub.

Progress & Results:

This project has been terminated. Results were presented as noted last interim report.

Work Unit No.: 4129 Interim Report

Title of Project: Antepartum Fetal Evaluation of Noise Evoked Fetal Heart Rate Response as an Indicator of Fetal Well Being.

Investigators:

Principal: James Haddock, MAJ, MC

Associates: Henry Klapholz, M.D., MAJ, MC

Objectives: To study the evoked heart rate patterns after the fetus is subjected to intrauterine sound stimulation at various intensities and relate the heart rate pattern response to fetal outcome.

Progress and Results: Fetuses were subjected to intrauterine sound stimulation at various intensities to pulsed sine-wave sound. Fetal heart rate reactivity as indicated by acceleration in fetal heart rate after exposure to sound was correlated to eventual fetal outcome. These fetuses were also subjected to the standard oxytocin challenge test and the results of these tests were compared to the fetal sound reaction pattern.

It was found that all fetuses that exhibited reactive sound stimulation patterns has negative oxytocin challenge tests. All these fetuses delivered in good condition. Those fetuses that did not appear to react to sound did well in general but a few had positive oxytocin challenge tests. It was concluded that a positive sound stimulation test may obviate the need for a formal oxytocin challenge test although more patients would have to studies to assure this with greater certainty.

This study will continue in an attempt to build up a larger volume patients since the importance of a negative oxytocin challenge test is still primary in the management of high risk patients. It is anticipated that fetal heart rate variability will be subject to analysis in the future. A protocol is being submitted for the development of the techniques for this. When this is developed, in cases where variability is poor suggesting compromise, it is a reasonable postulate that stimulus of the fetus through these noise arousal techniques will correct poor variability associated with fetal sleep and not that associated with compromise. This is to be tested.

Funding: No further funds this year.

Presentations: (1) Armed Forces District Meeting of the American College
of OB-GYN, Las Vegas, Nevada, September 1976.

(2) Published AJOB-GYN March 1978

Work Unit No: 4132

Title of Project: Prophylactic Antibiotics in Cesarean Section

Investigator: Patrick Duff, M.D., Major, MC

Objective: The purpose of the study was to evaluate the efficacy of prophylactic antibiotics in reducing infection-related morbidity associated with cesarean section.

Results: The study is complete. The results of the protocol demonstrate a statistically significant reduction in infection-related morbidity in patients who received a short perioperative course of antibiotics.

Conclusions: The experimental data and literature review support the use of prophylactic antibiotics in all patients undergoing repeat or primary cesarean section.

Funding Requirements: Travel expenses for author to present paper at future scientific meeting.

Type of Report: Complete.

Publications: (1) The paper will be presented at the AFD-ACOG meeting in Washington, D.C. in October, 1978.

(2) The paper will be submitted for publication to the Journal of Obstetrics and Gynecology.

Work Unit No.: 4134

Title of Project: Treatment of Women With Cervical Cancer Stage IIB, IIIB, IVA, and or Periaortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) Phase II

Investigators:

Principal: Robert C. Park, COL, MC

Associates: Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC; William Neglia, MAJ, MC

Objectives: Radiotherapy is the standard treatment for patients with advanced cervical carcinoma. The goal of this project is to determine if the addition of immunotherapy will enhance the radiation response rate.

Technical Approach: Patients are randomized to one of the two treatment regimens.

Progress & Results: To date, 77 patients have been entered in this GOG protocol.

Conclusions: No conclusions can be reached at this time, however, no marked adverse reactions have been found in the combination treatment arm.

Funding Requirements: No local funds are necessary as this is a GOG funded protocol.

Type of Report: Interim

Work Unit No.: 4135

Title of Project: A Randomized Comparison of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylenamine and Melphalan in Patients With Ovarian Adenocarcinoma: Suboptimal Stage III, Stage IV, and Recurrent Equivalent to Stage III and IV (Phase 3)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC; Jeffrey Weisbaum, MAJ, MC, Johannes Blom, MD

Objectives: Single alkylating chemotherapy agents produce a 30% response rate in patients with epithelial ovarian cancer. The objective of this study is to determine if adding Adriamycin or Hexamethylenamine will enhance the response rate.

Technical Approach: Patients are randomized to one of the three treatment arms. 1) Alkeran; 2) Alkeran plus Hexamethylenamine; 3) Cytosan plus Adriamycin.

Progress and Results: A total of 259 patients have been entered into this protocol from the entire GOG; 14 from Walter Reed. It is too early for specific statistical analysis; however, at the present time, there is no difference in overall response rate, but there is a marked difference in complete response for both combination arms. Hexamethylenamine is an investigational drug - to date there have been no adverse reactions observed in any of the Walter Reed patients.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through GOG.

Type of Report: Interim

Work Unite No.: 4136

Title of Project: A Randomized Comparison of Melphalan Alone Versus Melphalan Therapy Plus Immunotherapy in the Treatment of Women with Stage III (Optimal) Epithelial Carcinoma of the Ovary.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC; Johannes Blom, MD

Objectives: Melphalan alone produces a 30% response rate in patients with epithelial cancer. The objective of this study is to determine if the additional of immunotherapy will enhance the response rate.

Technical Approach: Patients with optimal Stage III epithelial ovarian carcinoma are randomized to one of two treatment regimens. Regimen #1 is Alkeran alone and Regimen #2 is Alkeran plus C-Parvum.

Progress & Results: To date, 69 patients have been entered in this GOG protocol. No statistical differences in the two treatment regimens are noted at the present time. In addition, no severe reactions have been noted in either treatment arm.

Conelusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through the GOG.

Type of Report: Interim

Work Unit No.: 4137

Title of Project: A Randomized Comparison of Pelvic and Abdominal Radiation Therapy Versus Pelvic Radiation and Melphalan Versus Melphalan Alone in Stage II Carcinoma of the Ovary (Phase III)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC; William Neglia, MAJ, MC; Johannes Blom, MD

Objectives: The standard treatment for patients with Stage II ovarian carcinoma has been postoperative irradiation. Recent data supports that single alkylating chemotherapy is equally effective. The objective of this study is to determine if radiation alone, chemotherapy alone, or combinations of the two are the best treatment methods for this disease.

Technical Approach: Patients are randomized to one of the three treatment arms.

Progress & Results: This protocol accrues patients from GOG, RTOG, and ECOG. To date, 36 patients have been entered. It is too early for a statistical analysis.

Conclusions: None at present.

Funding Requirements: No local funds are necessary as this is a GOG funded protocol.

Type of Report: Interim

Work Unit No. 4138

Title of Project: Diagnosis and Treatment of Intrauterine Abnormalities Using the Hysteroscope

Investigator: Thomas A. Klein, LTC, MC

Objectives: To evaluate the feasibility of using the hysteroscope in in-patients and out-patients to establish a valid diagnosis in cases of abnormal uterine bleeding and habitual abortion.

Technical Approach: Hysteroscopy was to accompany all cases requiring diagnostic D & C in patients under 40 years of age. Results of hysteroscopically obtained biopsy were to be compared to results of conventional curettage. Logistics and patient acceptance of outpatient hysteroscopy were to be evaluated by questionnaire.

Progress and Results: The protocol has not been activated because of logistical problems and lack of availability of appropriate equipment.

Conclusions: None at present

Funds Utilized, FY-78: None

Funding Requirements, FY-79: None anticipated at present

Type of Report: Interim

Work Unit No.: 4139

Title of Project: A Randomized Comparison of melphalan, 5FU and Megase Versus Adriamycin, Cytosan, 5FU and Megase in the Treatment of Patients With Primary Stage III, Primary Stage IV, Recurrent or Residual Endometrial Carcinoma (Phase III)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Johannes Blom, MD; Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC

Objectives: To determine the efficacy of multi-drug preparations in the treatment of high-risk endometrial carcinoma and to see if one of two programs, previously shown by phase studies, is superior.

Technical Approach: Patients with advanced or recurrent endometrial carcinoma are randomized to one of two treatment regimens.

Progress & Results: To date, 164 patients have been entered in this GOG protocol. No statistical differences, as yet, are shown.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is GOG sponsored.

Type of Report: Interim

Work Unit No.: 4140

Title of Project: A Clinical-Pathologic Study of Stage I and II Carcinoma of the Endometrium.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Paul B. Heller, MAJ, MC; Roger Lee, LTC, MC; Jeffrey Weisbaum, MAJ, MC

Objectives: To determine the incidence of pelvic and aortic lymph node metastasis and the relationship of these node metastasis to other important prognostic factors in patients with adenocarcinoma of the endometrium.

Technical Approach: All patient with Stage I and II adenocarcinoma of the endometrium who are medically and surgically fit, have primary surgery to include TAH-BSO and pelvic and aortic lymph node sampling. The patients then are placed on additional therapy depending on the pathologic findings.

Progress & Results: 201 patients are entered in this GOG study; 11 from Walter Reed. The study is too early for statistical analysis.

Conclusions: None

Funding Requirements: No local funds are necessary as this is a GOG funded protocol.

Type of Report: Interim

Work Unit No.: 4141

Title of Project: A Randomized Study of Adriamycin as an Adjuvant After Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma, Stage I and Occult Stage II.

Investigator:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, MAJ, MC; William Neglia, MAJ, MC; Johannes Blom, MD; Jeffrey Weisbaum, MAJ, MC

Objectives: To study the differences in morbidity in patient survival as functions of the various tumor growth patterns in patients with poor-risk endometrial carcinoma.

Technical Approach: Patients are selected for this protocol by extent of disease determined at surgery. Those who have a greater than 1/2 myometrial invasion or extra uterine spread all receive radiation therapy. Following this, there is randomization to Adriamycin or no further treatment.

Progress & Results: To date, 15 patients have been entered in this GOG study; 1 from Walter Reed. It is too early to give any statistical analysis.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through GOG.

Type of Report: Interim.

WORK UNIT #: 4501

TITLE: Clinical Evaluation of Fluorescence Scanning of the Thyroid with Americium 241 Source

INVESTIGATORS: *Merrill C. Johnson, COL MC
*Robert J. Corcoran, LTC MC

PROGRESS & RESULTS:

In addition to the patients with untreated Graves' disease reported in fiscal year 1977, we have encountered a number of patients with this disease who were under treatment. Patients on medical therapy longer than six months who were euthyroid averaged 3.3 mg. thyroidal iodine. In five patients persistently hyperthyroid after the same length of medical treatment, the average was 17.3 mg. Six months after treatment with radioactive iodine (^{131}I), five patients were found to be euthyroid and their thyroidal iodine content averaged 1.7 mg. Four patients were hypothyroid and on thyroid hormone replacement. In this group, glandular iodine was either nondetectable or present in trace amounts. One patient was still hyperthyroid six months after treatment with radioactive iodine and in this individual, the thyroidal iodine content was 17.0 mg. Seven patients with primary hypothyroidism and no history of previous treatment were seen. They were similar to patients rendered hypothyroid after radioactive iodine therapy in that none had more than trace amounts of thyroidal iodine.

CONCLUSION:

Although the clinical role of fluorescence iodine quantification remains to be fully established, the technique provides information not otherwise available on an important parameter of thyroid status.

FUNDS REQUESTED: (FY 79) \$1,500.00

PUBLICATIONS: (FY 78) Solitary Autonomous Thyroid Nodules: Comparison of Fluorescent and Pertechnetate Imaging. J Nuc Med, 18:1064-1068, 1977.

Quantitative Thyroid Fluorescent Scanning: Technique and Clinical Experience. Am J Roentgenology, 130:517-522, 1978.

Discordant Imaging of a Thyroid Nodule with ^{131}I and $^{99\text{m}}\text{Tc}$: Concordance of ^{131}I and Fluorescent Scans. Radiology, 128:705-706, 1978.

TYPE OF REPORT: Interim

*Principal investigator has been replaced by Robert J. Kaminski, MAJ MC and the Associate investigator by Isamu Y. Kang, LTC MC.

WORK UNIT #: 4502

TITLE OF PROJECT: Plasma Angiotensin Levels and Response to Antihypertensive Therapy in Essential Hypertension

INVESTIGATORS : Robert J. Corcoran, LTC, MC
Jules Bedynek, COL, MC
Robert J. Kaminski, MAJ, MC

PROGRESS & RESULTS: This project was terminated on retirement of the principal investigator. See previous report for results.

TYPE OF REPORT : FINAL

WORK UNIT #: 4514

TITLE OF PROJECT: Clinical Evaluation of ¹¹¹Indium DTPA

INVESTIGATORS: Merrill C. Johnson, COL, MC
Robert J. Corcoran, LTC, MC

PROGRESS AND RESULTS: A total of 12 radiocisternograms were performed on 11 patients during the past year. After review and correlation with clinical, pathological and radiographic findings, there were 7 positive results, 4 normal and 1 unsatisfactory.

Since the inception of this study, a total of 48 patients have been studied with 34 positives, 15 negatives, 4 unsatisfactory and 1 suspicious. There were no known false positives or false negatives. There were no cases of adverse reactions.

CONCLUSIONS: Radiocisternograms continue to be the study of choice in evaluating CSF dynamics and are of particular value in the diagnosis of CSF leaks and in evaluating shunt potency.

TYPE OF REPORT: INTERIM.

WORK UNIT #: 4515

TITLE OF PROJECT: Broad Clinical Evaluation of 99m Technetium Labeled Stannous Glucoheptonate as a Diagnostic Agent for Studying the Kidney.

INVESTIGATOR: Merrill C. Johnson, COL, MC

PROGRESS AND RESULTS: Since the Annual Report for 1977, there were an additional 21 patients studied using the radiopharmaceutical 99m Technetium Glucoheptonate for the detection of renal parenchymal abnormalities.

A total of 30 patients have been studied under this protocol and while the correlation with other diagnostic modalities appeared excellent, the small number of patients studied precludes an adequate assessment of this material as a diagnostic aide in evaluation of renal abnormalities.

In February 1978, this radiopharmaceutical was released by the FDA for general diagnostic use and consequently this project was terminated as of that date.

CONCLUSION: 99m Technetium Glucoheptonate appears to be an excellent agent for the radionuclide evaluation of renal parenchymal abnormalities.

TYPE OF REPORT: FINAL.

WORK UNIT #: 4518

TITLE OF PROJECT: Clinical Evaluation of 99mTc Electrolytically Labeled Human Serum Albumin

INVESTIGATORS: Merrill C. Johnson, COL, MC
Robert J. Corcoran, LTC, MC

PROGRESS AND RESULTS: This project was terminated on the retirement of the principal investigator. See previous report for results.

TYPE OF REPORT: FINAL

WORK UNIT #: 4519

TITLE OF PROJECT: Study of Thallium Chloride Tl-201 for Myocardial Imaging in Acute Infarction and/or Ischemia

INVESTIGATORS: Merrill C. Johnson, COL, MC
Robert J. Corcoran, LTC, MC

PROGRESS AND RESULTS: Thallium-201 has been released by the FDA for routine clinical use. This project was terminated since the release of the isotope coincided with its initial use at WRAMC.

TYPE OF REPORT: FINAL.

Work Unit No. :4601

Title of Project : Participation in the National Cooperative
Study of Early Hodgkin's Disease

Investigators :

Principal Investigator : George B. Hutchison, M. D. Project
coordinator at Harvard School of Public Health.
Associate Investigator : Johannes Blom, M. D. and William
Neglia, M. D. at Walter Reed Army Medical Center.
29 associate investigators at other collaborating centers.

Objectives : To determine the effects on survival, disease extension, and complications of therapy of differing irradiation volumes in treatment of early staged Hodgkin's disease.

Technical Approach : This clinical trial study was randomized and prospective, comparing localized irradiation to clinically involved region with extended field irradiation to clinically involved region plus regions suspected of being sites of sub-clinical disease.

Progress and Results : An interim report was distributed February, 1978. Localized recurrences have appeared in significantly greater frequency in patients receiving localized treatment than in those given extended field therapy. Extensions to extra-nodal sites on the same side of the diaphragm as the initial disease are also more frequent with localized treatment, but the excess is smaller, and transdiaphragmatic extensions are only slightly reduced by extended field therapy. There is no significant survival difference between the two therapy groups for the total collaboration, and for the Walter Reed series there is a non-significant reduction in mortality in the group given localized therapy. Entry of patients into this study was terminated in 1971 at Walter Reed and in 1973 for the entire collaboration. At a meeting of all participating institutions held in Chicago, July, 1976, it was decided that follow-up of 10 years or more might be needed to conclude the study. The survival of both groups is substantially better than projected in 1967, at the outset of the study and based on reports available at that time.

Conclusions : To date, comparison of localized fields with extended fields in therapy of early Hodgkin's disease has not shown a clear superiority of either technique within 10 years of follow-up. The study suggests that extensions following extended field therapy may routinely carry a poor prognosis but that local extensions following local field therapy may be followed by cure in a substantial proportion of cases.

Publications :

1. Hutchison, G. B. Progress report. Hodgkin's Clinical Trial, 1972. National Cancer Institute Monograph No. 36:387-393. 1973.
2. Nickson, J. J. and Hutchison, G. B. Hodgkin's disease clinical trial. Sixth National Cancer Conf. Proc. 1968. Pages 77-81. Lippincott Philadelphia. 1970.
3. Nickson, J.J. and Hutchison, G. B. Extensions of disease, complications of therapy, and deaths in localized Hodgkin's disease; preliminary report of a clinical trial. Am. J. Roentg., Rad. Th., Nuc. Med. 114: 564-573. 1972.
4. A collaborative study. Report prepared by Hutchison, G.B. on behalf of Steering Committee. Survival and complications of radiotherapy following involved and extended field therapy of Hodgkin's disease, stages 1 and 2. Cancer 38:288-305. 1976.

Funding requirements :

Authorized FY 78: \$760

FY 79:

Travel : \$750

HARVARD UNIVERSITY
SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF EPIDEMIOLOGY

677 Huntington Avenue
Boston, Massachusetts 02115
(617) 732-1050

October 12, 1978

Dr. William J. Neglia
Chief, Radiation Therapy
Department of Radiology
Walter Reed General Hospital
Washington, D. C., 20012

Dear Dr. Neglia,

Enclosed is a progress report which you may use for the purposes of the Clinical Investigation Committee. I hope this is in order and contains the information you need.

Best regards to you.

Sincerely,

George B. Hutchison

George B. Hutchison
Professor of Epidemiology

Encl. Progress report

GBH/lm

WORK UNIT NO: 5501

TITLE OF PROJECT: Incidence of Hemolytic Disease of the newborn due to ABO Incompatibility (ABO/HDN at Walter Reed Army Medical Center.

INVESTIGATORS: Bobby F. Chaney, CPT, MSC
Ronald C. Vura, CPT, USAF, BSC

OBJECTIVES: To determine retrospectively, through the investigation of patient statistics, medical records and laboratory data, the incidence of ABO/HDN at WRAMC. Further to compare this incidence with that reported at National Naval Medical Center, Bethesda and in the literature.

TECHNICAL APPROACH: The pediatric log book of births for the period 1 Sept 72-31 Dec 76 was correlated with the Blood Bank's serology results for the same period.

PROGRESS AND RESULTS: Clinical and Serological results for 2500 births have been recorded from WRAMC and compared with similar results for 3241 births recorded at NNMCC, Bethesda.

CONCLUSIONS: See attached student paper. (Incl. 2)

FUNDS UTILIZED FY 77: NONE

FUNDING REQUIREMENTS FY 78: NONE

PUBLICATIONS: Attached Student Paper submitted to Education Supervisor for grade.

TYPE OF REPORT: FINAL

Work Unit No.: 6017

Title of Project: Clinical Studies in Thermometry

Investigators:

Principal: Lewis B. Harden, LTC MC

Associates: Robert Mesrobian, CPT
Doreen Roberts, RN
Virginia Leaper, LPN

Objectives: To obtain data for the evaluation of routine procedures used in thermometry as presently practiced on pediatric outpatients. Specifically we are asking, "Can axillary temperatures be used in patients up to age 4 without loss of accuracy when compared to the rectal temperature?" A single use chemical thermometer is also being tested for accuracy at both axillary and rectal sites.

Technical Approach: A crossover design allows each patient to act as their own control while comparing axillary and rectal measurements. A rectal temperature taken at 3 minutes with a glass reference thermometer serves as the standard for comparison of values. Axillary temperatures with a glass reference thermometer and both axillary and rectal measurements with the single use thermometer are then analyzed for variation from the standard.

Presentation: "Thermometry, Does the Axilla Measure Up?" was presented at the Tri-Service Pediatric Seminar, San Francisco, California, in March 1978, by Doreen Roberts, RN.

If data is published in future, we will present to Clinical Investigation Service.

Type of Report : Termination

Work Unit No. 6018

26 October 1978

PROJECT TITLE: Newborn Host Defenses: I Developmental Aspects of Newborn Neutrophil Chemotaxis

INVESTIGATORS: Principal Alan D. Mease
Associate Frederick B. Ruymann

OBJECTIVES: This project is designed to confirm and characterize the cellular chemotactic defect of the newborn neutrophil and to correlate this decrease with gestational age and birth weight. Do preterm infants have a more severe decrease in neutrophil chemotaxis than term infants?

TECHNICAL APPROACH: The Cr⁵¹ labelled technique of Gallin is being used to measure neutrophil chemotaxis in cord blood specimens of infants of various gestational ages and birth weights.

PROGRESS AND RESULTS: The technique of Cr⁵¹ neutrophil chemotaxis has been learned in the laboratory of John Gallin and applied to the study of neutrophils from the cord blood of 16 term infants. These studies were done in his laboratory by the principal investigator (ADM) and have confirmed the existence of decreased chemotaxis. These studies found no evidence of a serum inhibitor to chemotaxis in cord blood serum indicating that decreased newborn neutrophil chemotaxis is due to an intrinsic cellular difference. These results were reported in last years progress report and no new chemotactic studies have been done. Most of this year was spent in getting the laboratory in the NMTF set up to do Cr⁵¹ labelled chemotaxis with regard to appropriate equipment, supplies etc. We have just received our first shipment of Cr⁵¹ and plan to continue to do these studies of neutrophil chemotaxis.

Since the chemotactic studies have been done in Gallin's laboratory we have gained additional experience in working with newborn neutrophils. Preliminary studies suggest that the viability of the newborn neutrophil in vitro may be decreased. Therefore Gallin's technique will be modified to measure chemotaxis over shorter incubation times using micro-pore filters with larger pore size.

We have also done preliminary sizing studies of newborn neutrophils which suggest that they are smaller than adult neutrophils.

These observations suggest the modification of incubation time and filter pore size may have important implications in the measurement of newborn neutrophil chemotaxis. Such studies are planned as well as continued studies of chemotaxis than cord blood of infants of various gestational ages.

CONCLUSIONS: Newborn neutrophil chemotaxis is decreased as measured by the chromium labelled technique of Gallin but the nature of the decreased measured chemotaxis need further studies in which the technique is modified. No data is yet available regarding changes in measured chemotaxis with gestational age but this will be obtained throughout the coming year.

FUND UTILIZED, FY-78

\$2500

FUNDING REQUIREMENTS FY-79

Personnel Doris Burgess civilian 16hrs/wk 1 yr

Equipment

none

Supplies

\$1500

Travel

500

Publications: Newsletter, Section on Military Pediatrics, American Academy of Pediatrics, page 3, May 1978.

Presentations: Identification of a newborn neutrophil membrane abnormality using PHA-induced neutrophil aggregation, Uniformed Services Pediatric Seminar, San Francisco, California, March 1978.

Type of Report: Interim

1. Work Unit N.: 6021
2. Title of Project: The Role of Leutinizing Hormone Releasing Hormone (LHRH) in Evaluation of the Hypo-halamic Pituitary Gonadal Axis in Children
3. Principal Investigator: LTC Chandra M. Tiwary, MC
4. Objective: To develop a test for assessing hypothalamic-hypophyseal gonadal axis in children which can be used on an outpatient basis.
5. Progress and Results: The measurement of hormones for the protocol was assigned to Hazelton Laboratories, the contractual approval with laboratory was intimated to me in April 1978 and the clinical studies were started (the LHRH supply arrived in March/April 1978). Twenty-two children have been studied. Serum samples have been analysed on eleven of these children. The samples on the other 11 children are in storage and will be analysed on the release of funds.

Preliminary analysis of the data on the 11 children suffering from a variety of disorders follows:

- I. The LH response to LHRH was minimal in premature adrenarche (2 out of 2 cases), moderate in premature thelarche (1 out of 1 case), and marked in precocious puberty (2 out of 2 cases).
- II. The FSH response to LHRH was not different between patients with premature adrenarche and precocious puberty. The FSH response in the single case of premature thelarche was very marked.
- III. Patients with hypogonadism (2 cases) had shown minimal LH response to LHRH although FSH response (probably a function of age) is moderate.
- IV. One girl (SS) exhibited the highest FSH (215 mIU/ml) and LH (90 mIU/ml) response to LHRH ten years ago this girl had recieved cancer chemotherapy and irradiation to pelvic area for a rhabdomyosarcoma. This treatment probably damaged her ovaries.
- V. A few children showed a rise in serum gonadatropin which was more marked following the third injection of LHRH than after the first injection. This indicates that a poor response after the first of LHRH does not necessarily indicate a pituitary lesion. The disparity in gonadotropin response following first and third injection of LHRH might indicate a hypothalamic disturbance.

6. Confirmation of the above findings on a large sample is required and would (a) help in early differentiation and diagnosis of a child with precocious puberty from that with premature adrenarche or premature thelarche; decision regarding appropriate therapeutic intervention can also be made early; (b) provide a harmless and simple means of differentiating hypothalamic from pituitary lesion; (c) detect; minor gonadal lesions.
7. Request for minor addition to the protocol: We are measuring serum gonadotropins in 6 samples which are taken 0', 30', 60', 90', 120', and 240', after the injection of LHRH. We would like to measure the serum gonadotropins in an additional pooled sample collected from aliquots (2ml) taken from each of the 5 (excluding the 0' sample) serum samples. If a good correlation between the level of serum gonadotropins in this additional (pool) sample and the mean of the individual samples is found, it will suggest that one measurement of serum gonadotropin will appropriately show the LHRH response. This will decrease sample analysis cost by 80%. A preliminary report from the laboratory of Dr. Santen (Ann. Int. Med. 1978;89:512-3) suggests that in adults the serum pool LH and FSH measurements give a very good estimate of gonadotropin status even though the LH and FSH levels are rapidly changing after LHRH stimulation. They reported highly significant correlation for both LH ($r = .988$) and FSH ($r = .984$) when mean and pool measurements of the incremental increase after LHRH are compared.
8. Extra cost of the addendum to the protocol: The cost of gonadotropin analysis of the additional sample per subject will be \$26.00. The total cost per subject will increase from \$284.00 (original cost) to \$310.00. This represents an increase of 5.6%.
9. Funds requested for FY 1979: Sample analysis: \$310.00 per subject, (14 samples for LH, FSH and 4 samples for testosterone and estrogen measurement), x 40 subjects ----- \$12,400.00

Pipets, tubes, etc	200.00
Preparation of paper etc	150.00
Presentation of paper travel etc	600.00
TOTAL	13,350.00
10. Funds requested for FY 1978: 110 samples analysed for LH and FSH, and 80 for testosterone and estrogen----- \$2,723.00

Funds not used	9,177.00
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11. Publication - None
12. Travel - None
13. Type of Report: Interim

Work Unit No. 6023

TITLE: Newborn Host Defenses II. Studies of the Newborn Neutrophil Membrane
Using Lectins as Molecular Probes.

INVESTIGATORS: Principal - Alan D. Mease
Associate - Gerald W. Fischer
Askold Mosijczuk (until 7/78)
Frederick B. Ruymann

OBJECTIVE: Experimental evidence suggests that the binding of chemotactic factors to the cell membrane precedes and is essential to the initiation of directional movement. Directional movement of the newborn neutrophil is impaired despite normal random movement. The membrane of the newborn neutrophil is less deformable than that of the adult neutrophil membrane. These observations suggest that the etiology of the newborn neutrophil's decreased chemotactic responsiveness might be unique membrane properties which effect the binding of chemotactic factors to the cell membrane. The objective of this project is to investigate the membrane properties of the newborn neutrophil using the plant lectin PHA which binds to specific oligosaccharide receptors on the cell membrane and forms cross bridges between cells thus producing aggregation.

TECHNICAL APPROACH

PHA-induced aggregation of adult and newborn neutrophils is being investigated using standard aggregometry techniques. See methods section of enclosed paper and abstracts for details of techniques and experimental design.

PROGRESS AND RESULTS

Our studies to date demonstrate that newborn neutrophils have impaired PHA-induced aggregation suggesting membrane properties which differ from adult neutrophils. These differences have not previously been reported and may have functional implications. See Results section of enclosed paper for details.

The biochemical nature and function implications of these abnormalities remains to be determined. In an attempt to find morphologic clues to these abnormalities of the newborn neutrophil cytologic studies were done. In the absence of Ca and Mg the mean percentage of newborn neutrophils with membrane projections was less than that of adult neutrophils. Ca and Mg reduced membrane projection in adult neutrophils to newborn levels. These findings suggest that newborn neutrophils have an inability to undergo conformational membrane changes in response to alterations in Ca and Mg balance. Since membrane regulation of Ca and Mg flux is important in chemotaxis, a newborn neutrophil membrane abnormality affecting this flux may be related to decreased newborn neutrophil chemotaxis.

In an attempt to determine the biochemical nature of this abnormality and more specifically to evaluate the role microtubular function, the effect of the antitubulin, vinblastine (VBL) or lectin-induced neutrophil aggregation was studied. VBL decreased adult PHA-induced aggregation to newborn levels suggesting impairment in microtubular function could explain unique newborn neutrophil membrane characteristics.

CONCLUSION

Unique membrane characteristics of the newborn neutrophil have been documented and preliminary evidence suggests the possibility of these being due to microtubular dysfunction.

Funds Utilized FY-78 excluding tech \$6500

Funding Requirement FY-79

Personnel Doris Burgess Civ. tech. 8 hr/wk 1 yr	
Equipment - None	-
Supplies	\$2500
Travel	500

Publications

Mease AD, Fischer GW, Mosijczuk AD, Ruymann FB, Landes D. Identification of a neutrophil membrane difference between adult and newborn cells using a lectin-induced assay. Pediatric Research 12:483, 1978 (Abstract)

Mease AD, Burgess DT, Fischer GW, Ruymann FB. Decreased hypocalcemic and hypomagnesemic blebbing of newborn neutrophils. Pediatric Research 12:483, 1978 (Abstract)

Mease AD, Fischer GW, Ruymann FB. Decreased phytohemagglutinin-induced aggregation of human newborn neutrophils. (Submitted to Pediatric Research)

Presentations

Identification of a newborn neutrophil membrane abnormality using PHA-induced neutrophil aggregation. Uniformed Services Pediatric Seminar. San Francisco, California. March 1978. This paper won the Ogden Bruton Award for Military Pediatric Research.

Identification of Newborn neutrophil membrane differences between adult and newborn cells using a lectin-induced aggregation assay. Society for Pediatric Research. New York City, New York, April 1978. POSTER SESSION.

Type of Report: Interim

Work Unit No. 6024

TITLE: Newborn Host Defenses III: Phagocytosis and Killing of Group B Streptococci

INVESTIGATORS: Principal Alan D. Mease
Associates Gerald Fischer
George Lowell
Frederick Ruymann
James Bass

OBJECTIVES: The purpose of this project is to establish a reproducible bacteriocidal assay for Group B Streptococci and evaluate the ability of cord blood neutrophil to kill Group B Streptococci.

TECHNICAL APPROACH: See materials and methods section in enclosed article. Neutrophils isolated from cord blood will be studied and their ability to kill Group B Streptococci compared to adult neutrophil in each experimental condition.

PROGRESS & RESULTS: The technique has been worked out using five different strains of streptococci and is reproducible. At present we are just beginning to study newborn neutrophils with this assay.

CONCLUSION: A reliable neutrophil opsonophagocytic bactericidal assay has been worked out and will be applied to the study of newborn neutrophils.

FUND Utilized, FY-78 \$2000

Funding Requirements, FY-79

Personnel Doris Burgess civilian tech 8hr/wk 1 yr	
Equipment	none
Supplies	\$1000
Travel	500

Publications: Fischer GW, Lowell GH, Crumrine MH, Bass JW. Demonstration of opsonic activity and in vivo protection against group B Streptococci Type III by Streptococcus pneumoniae type 14 antisera. J. Exp. Med. 148:776-786, 1978.

Type of Report: Interim

1. Work Unit Number 6025

2. Title of the Project: Role of surface tension measurement of amniotic fluid lipid extract in prediction of development of RDS in neonates.

3. Investigators:

Principal: Chandra M. Tiwary, M.D., LTC, MC
Associates: Richard D. Landes, M.D., LTC, MC
James B. Haddock, M.D., MAJ, MC

Objective: To measure surface tension of amniotic fluid lipid extract prior to and during labor, and to correlate it with the subsequent development of RDS in newborn.

Progress and Results: I am collecting the clinical data of amniotic fluid. We have in storage about 75 sample, these will be analysed when the apparatus for the surface tension determination becomes available. The apparatus is expected to be received in December 1978. I shall start measurement of the surface tension of the stored and current samples.

Funds utilized - FY 1978:

Personnel	Chandra M. Tiwary
Equipment	None
Supplies	\$653.00
Travel	None
Other	None
Fund not used	6,597.00

Funds requested FY 1979

Personnel	-	
Equipment	-	\$6,750.00
Supplies	-	250.00
Travel	-	600.00
Paper, Preparation, Publication and reprints		150.00
	TOTAL	<u>\$7,750.00</u>

Type of Report: Interim

1. Work Unit Number 6026

2. Title of the Project: Tracheal Aspirate surface tension as prognostic indicator in infants with Respiratory Distress Syndrome (RDS)

3. Investigators:

Principal: Chandra M. Tiwary, M.D., MC, LTC

Associate: Richard D. Landes, M.D., MC, LTC

4. Objective: To measure the surface tension of the lipid extract of tracheal aspirate at various periods and to use this data in evaluating the prognosis of newborn with respiratory distress syndrome (RDS).

5. Progress and Results: The apparatus for measurement of the surface tension has not been received (according to the supplier. There has been a manufacturing delay). We hope to receive the apparatus in December 1978 and start the study .

We can not store the tracheal aspirate (it is likely to be contaminated). because of its alteration by the bacteria or fungus. This may alter the surface tension property of the fluid.

* Funds utilized - FY 1978:

Personnel	Chandra M. Tiwary
Equipment	None
Supplies	None
Travel	None
Other	None
Funds not used	

Funds requested FY 1979:

Personnel	-	Chandra M. Tiwary
Equipment		
Supplies		\$650.00
Travel		600.00
Paper, Preparation, Publication and reprints		150.00
		<hr/>
		\$1,400.00
Type of Report: Interim	TOTAL	

Work Unit No.: 7105

Title of Project: Study of CEP Responses in Pediatric Epileptic Patients before and after Withdrawal of Anticonvulsants.

Investigator: Archer D. Huott, COL MC

Objectives: To develop technique for prediction of favorable prognosis regarding pediatric epileptic patients after anticonvulsant drug withdrawal.

Technical Approach: This study is essentially a comparison of a child's prior CEP's before and after withdrawal of anticonvulsant drugs in those epileptic patients meeting the following criteria:

- a) Onset of idiopathic epilepsy afebrile seizures below the age of 12.
- b) Freedom of minor or major seizures for a period of two years.
- c) Normal awake EEG with sleep, hyperventilation, and auditory and stroboscopic activation.

It is felt that by such a study those patients who will eventually relapse will be detected early enough to reinstitute therapy and prevent the resumption of clinical seizures.

Progress and Results: Continued technical problems necessitate termination of project. If resumed in the future, new protocol will be submitted.

Work Unit No.: 7109

Title of Project: The Application of Somatosensory Spinal Evoked Response in Spinal Cord Pathology.

Investigator: Archer D. Huott, COL MC

Objectives: To correlate clinical evoked level of lesion with finding at operation. Also, to obtain normative data.

Technical Approach: Somatosensory input in the form of electrical shocks to the nerves of the leg and pickup of these potentials over the spinal cord at various levels and also over the somatosensory cortex. This analysis utilizes computer technology.

Progress & Results: Continued technical problems necessitate termination of this project. Future protocols will be submitted if felt indicated.

Work Unit No.: 7111

Title: Interruption of Maintenance Neuroleptic Therapy.

Investigators: R. Harlan Bridenbaugh, LTC, MC

Objective: To determine the immediate and long term results of interrupting maintenance neuroleptic therapy, to compare three and twelve week schedules for tapering neuroleptic therapy, and to determine the relationship between serum prolactin and clinical status during reduction of neuroleptic therapy.

Technical Approach: Systematic evaluation of patient's mental status and psychosocial functioning by standardized rating scales. Monitoring of serum prolactin levels during tapering and after discontinuance of maintenance neuroleptic therapy.

Progress and Results: Three (3) patients have been entered in the project and have completed the required series of blood tests and psychosocial evaluations. Serum prolactin levels were performed on blood samples that had been kept frozen at -70° C. All values obtained were within the normal range.

Conclusions: Patients entered into the project thus far have apparently been on maintenance neuroleptic medication in doses that are too low to raise serum prolactin levels. Clinical implications at this point cannot be made because only a small number of patients have been studied. Many factors have made it difficult to obtain patient entry thus far. It is expected that two more years will be required to obtain adequate patient material.

Funds Utilized, FY-78: 18 serum prolactin measurements - \$72.00

Funding Requested, FY-79: None.

Publications: None.

Type of Report: Interim.

WORK UNIT NO: 7151

TITLE OF PROJECT: Cognitive Components of Interpersonal Functioning in
Brain Damaged Adults

PRINCIPLE INVESTIGATOR: David H. Edwin, Graduate Student
Psychology Department, University of Maryland

OBJECTIVES: The purpose of this study is to develop a psychometric tool for assessing the cognitive components of interpersonal functioning which may be impaired in brain damaged adults. Specifically, the aims of the research are threefold:

1. To develop an alternative scoring system for the Picture Arrangement subtest of the Wechsler Adult Intelligence Scale (a standardized test of intelligence) that will identify and differentiate cognitive processes believed to be basic to interpersonal functioning.
2. To understand the nature of impairment in social cognition by comparing brain damaged and non brain damaged populations.
3. To compare and discriminate between different kinds of difficulties in social cognition evidenced by stroke patients with right hemisphere brain damage as contrasted with patients with left hemisphere brain damage.

PROGRESS AND RESULTS: Project has been terminated because of lack of subjects who meet criteria for study.

CONCLUSIONS: None.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Final

Work Unit No.: 7212

Title: RBC Lithium Concentration and Clinical Correlates.

Investigators: R. Harlan Bridenbaugh, LTC, MC
James G. Hunter, CPT, MC
John L. Wamble, MAJ, MC

Objective: To establish WRAMC norms for RBC lithium concentration, and to determine clinical correlates (treatment response, side effects) of RBC lithium concentration and RBC to plasma ratios.

Technical Approach: N/A. RBC lithium analyses were discontinued in May 1977.

Progress and Results: N/A.

Conclusions: There have been a number of negative reports recently published in the psychiatric literature. The Principal Investigator is terminating this project as it is very unlikely to yield clinically useful information.

Funds Utilized, FY-78: None.

Funding Requested, FY-79: None.

Publications: None.

Type of Report: Terminated.

Work Unit No.: 7214

Title: Pre- and Post-Discharge Assessment of Psychiatric Patients

Investigators: Donald W. Morgan, COL, MC
R. Harlan Bridenbaugh, LTC, MC
Emmanuel Cassimatis, MAJ, MC
Charles R. Privitera, MAJ, MC

Objective: To establish, within the Psychiatry Service, WRAMC, a structured method of assessing pre- and post-discharge levels of psychosocial function of psychiatric patients seen by a Medical Evaluation Board (MEB); to compare pre-discharge morbidity with post-discharge function of psychiatric patients seen by an MEB; and to systematize the MEB procedure in order that training and education goals can be met.

Technical Approach: From Jan 77 to Aug 77, 200 consecutive patients seen by an MEB were entered into the study. Baseline psychological and demographic data were obtained while still on an inpatient status. Patients have been followed every three months by mailed questionnaires to monitor emotional and social-vocational functioning.

Progress and Results: The return rate for the questionnaires has been approximately 85%. Three patients have committed suicide. A wide range of outcomes are thus far apparent with about one-third of the group experiencing rehospitalization thus far. More detailed assessment will be carried out in the next 6-9 months.

Conclusions: It is feasible to follow patients by mail questionnaire. We will plan, at this point, to continue follow-up for three years from the time of discharge.

Funds Utilized, FY-78: None.

Funding Requested, FY-79: \$ 500.00

Publications, FY-78: None.

Type of Report: Interim.

Work Unit No.: 7215

Title of Project: Neuroendocrine Correlates in Depressive Disorders

Investigators: R. Harlan Bridenbaugh, LTC, MC
Charles R. Poling, LTC, MC
Robert L. Sack, M.D., Department of Psychiatry,
Stanford University Medical Center

Objectives: To determine serial MHPG excretion in patients being treated for depressive disorder, to determine correlations between diagnosis/treatment and MHPG excretion in depressive disorder, and to assess hypothalamo-pituitary-adrenal (HPA) axis function in depressive disorder.

Technical Approach: N/A.

Progress and Results: No patients have been entered into this project because investigators have been involved with other, higher priority work. Protocol is being terminated at this point.

Conclusions: N/A.

Funds Utilized, FY-78: None.

Funding Requested, FY-79: None.

Publications, FY-73: None.

Type of Report: Terminated.

Work Unit No.: 7217

Title: Management of Impairment of Accommodation Secondary to Psychotropic Medication

Investigators: R. Harlan Bridenbaugh, LTC, MC
Richard J. Sapolis, MAJ, ANC
Daniel L. LaDuke, CPT, ANC
Mary Barbara Papineau, CPT, ANC

Objective: To determine the incidence of impairment of accommodation secondary to the anticholinergic action of neuroleptics, tricyclic antidepressants, and anti-Parkinson agents; to evaluate the effectiveness of optical management of such impairment secondary to the above psychotropic agents; and to examine the relationship between dosage and degree of impairment of accommodation.

Technical Approach: Patients receiving psychotropic agents that have anticholinergic action are evaluated by means of a near vision reading card. If blurring of vision is noted at or inside a comfortable reading distance (16" - 20"), then patient is tried on + diopter eyeglasses in increasing increments of +0.5 diopter. Final strength of glasses dispensed is determined by patient choice alone. Level of medication is recorded and monitored and patients are re-evaluated at weekly intervals.

Progress and Results: Nineteen (19) patients have been formally entered into the project and a large number of patients (over 30 thus far) have been issued eyeglasses but not entered into the study. Screening was completed in June 1978 on Ward 108 on all patients receiving psychotropics with anticholinergic effect. Two-thirds of all patients showed evidence of impairment of accommodation.

Conclusions: Blurring of vision from the anticholinergic action of certain psychotropic agents is very prevalent on an acute treatment psychiatric ward. The immediate management is the same as for presbyopia, i.e., the application of + diopter reading glasses.

Funds Utilized, FY-78: None.

Funding Requested, FY-79: \$800.00

Publications, FY-78: None.

Type of Report: Interim.

Project No.: 8001

Principal Investigator: Jane G. Coffin

Title of Thesis: The Effect of a Diet Controlled in Gluten, Lactose,
Fat and Residue on Malabsorption Syndrome in Oncology
Patients Receiving Abdomino-Pelvic Radiation

Jane Gosselin Coffin, Master of Science, 1977

Thesis directed by: Eleanor R. Williams, Ph.D.
Associate Professor
Department of Food, Nutrition and Institution
Administration
and
Thelma S. Arnold, Maj., Ph.D.
Assistant Professor
School of Nursing
University of Maryland
Chief, Department of Nutrition
Walter Reed Army Institute of Nursing
Clinical Instructor
Department of Biochemistry
Uniformed University of Health Sciences

The effect of a diet restricted in gluten, lactose, fat and residue on malabsorption was determined using two groups of oncology patients receiving abdomino-pelvic radiation for various malignancies. One group followed the special diet, and the other the standard hospital diet. The diet was designed to reduce malabsorption in patients during radiotherapy. There were statistically significant differences between groups in B-carotene and D-xylose absorption, indicating that the test group, which had followed the special diet throughout radiotherapy, was better able to absorb B-carotene and D-xylose than the control group. While the occurrence of abnormal stools and vomiting did not significantly differ between groups, the amount of nausea experienced by the control group was

significantly greater. Since antidiarrheal agents were intermittently used in both groups, assessment of overall abnormal stool incidence was difficult. When data were adjusted for radiation dosage received, it was observed that the test group maintained a steady weight state regardless of radiation dosage. The control group, on the other hand, showed a tendency toward weight gain when radiation dosage was low, but as dosage increased, weight loss increased in a direct linear proportion.

Type of Report: Completed

Work Unit No: 8027

Title of Projects: Clinical Evaluation of Freeze-dried Bone Allographs in the Treatment of Severe Periodontal Osseous Defects

Investigators:

Principal: Ronald L. Van Swol, D.D.S.
Commander, Dental Activities, WRAMC

Associate: All Residents and Staff assigned to the Periodontia Service

Objectives: To evaluate the effectiveness of freeze-dried human bone allographs in the treatment of periodontal osseous defects.

Technical Approach: Consenting patients with large, severe periodontal osseous defects will be treated, using freeze-dried human bone allographs. Full thickness buccal and lingual flaps are developed in the surgical area, all granulation tissue is removed from the defect, the root surface is cleaned, and the osseous defect filled with the allograph material. The flaps are then repositioned and sutured to place. The surgical field is then covered with periodontal dressing and postoperative instructions given. The patient is seen in one week for suture removal and periodontal dressing change. At the two weeks postoperative time frame, the dressing is removed and home care instructions are given. The patient is then seen every 3 months for clinical and radiographic re-evaluation of the grafted area. At one year postoperatively, the area is re-entered for final evaluation and further grafting, if needed.

Progress and Results: During FY 78, 6 severe periodontal osseous defects were grafted. No complications were encountered in any of the cases, and good documentation was acquired in all instances.

Conclusions: During FY 78, we grafted 6 periodontal osseous defects. Our overall response has been of greater than 60% osseous regeneration, which has been very gratifying to the principal investigator. The use of this type of grafting material is now accepted by Periodontics as a non-experimental established material which may be used to treat severe

osseous defects.

4 Funding Requirements, FY 78: None, the personnel, equipment and staff (D.D.S.) of the Periodontia Service, Department of Dentistry, Walter Reed Army Medical Center were utilized.

Publications: None

Type of Report: Completed

Work Unit No.: 8029

Title of Project: The Effect of Patient Applied Fluoride on Dental Bacterial Plaque and Gingivitis: I. Toothbrush Delivery.

Principal Investigators: Ronald F. Godat, MAJ DC
Ronald L. Van Swol, COL DC
Dental Activities, WRAMC

Objective: The objective of this study is to determine whether a fluoride preparation can significantly reduce the amount of bacterial plaque and the severity of gingivitis when applied to the teeth daily by patients.

Technical Approach: Fluoridated dental preparations are currently in wide use and have been shown to significantly reduce the incidence of dental decay. Little attention, however, has been drawn to the ability of some of these compounds, notably stannous and amine fluorides, to effectively reduce dental plaque and gingivitis.

Past studies have been unable to demonstrate a correlation between the use of fluoride dentifrice and the reduction of dental plaque or gingivitis in patients. It is suspected that these fluoride applications have little effect on plaque for the following reasons.

a. None contain amine fluorides.

b. The stannous fluoride containing dentifrices not only have a very low concentration of the fluoride solution, but have it in an unstable aqueous solution. Therefore, the concentration of available fluorides in commercial dentifrices is often much lower than the manufacturer claims.

Conversely, stannous fluoride compounds available to dentists for topical application may reduce dental plaque and gingivitis because:

a. They are sold in nonaqueous solutions which are chemically stable.

b. Stannous fluoride has been shown to reduce or prevent bacterial colonization of enamel.

c. It has been a clinical observation at WRAMC Dental Clinic that patients in the Head and Neck Cancer Radiation Program who begin the daily self-application of a 0.4% Stannous Fluoride Gel preparation have a decreased severity of gingivitis and reduced dental plaque.

Conclusions: The research project was completed in June 1978 and is in the process of being revised for the last time prior to being submitted for publication. No further funding is necessary.

Type of Report: Completed

Work Unit No.: 8050

Title of Project: Immunity to Measles in a Military Population.

Investigators:

Principal: Leslie B. Altstatt, COL MC

Associate Investigators: Carlos C. Daughaday, Joel M. Dalrymple,
James C. Burke, and Richard Evans

Objectives:

a) To determine the susceptibility of certain active duty personnel to measles. b) To learn more of the basic mechanisms of acquired immunity.

Type of Report: Termination

Unforeseen obstacles have precluded implementation of this protocol. Termination of the protocol is appropriate.

Work Unit No: 9009

Title of Project: Abnormalities of B6 Metabolism and Glycogen Metabolism in Hodgkin's Disease

Investigators:

Principal: LTC Michael J. Haut, MD, MC
LTC John A. Kark, MD, MC

Associate: Johannes Blom, MD
LTC Jeffrey R. Berenberg, MD, MC
MAJ Salvatore Scialla, MD, MC
COL Robert W. Muir, MD MC

Objectives: B6 and glycogen metabolism are being investigated in tissues of patients with Hodgkin's disease in order to answer two questions: (1) Are the diminished levels of vitamin B6 coenzyme in Hodgkin's disease due to alterations in the enzymes regulating B6 metabolism? If so, in what tissues is B6 metabolism altered? (2) Does the deficiency of coenzyme B6 contribute to muscle weakness by decreasing the activity of muscle glycogen phosphorylase, a B6-containing enzyme.

During the past three years, we have concentrated almost entirely on the B6 metabolism aspects of this study, and are particularly interested in what controls plasma B6 levels in these patients.

Technical Approach: Our initial studies showed that some patients with Hodgkin's disease or other malignancies had lower plasma B6 levels than control subjects, but had increased capability for red cell conversion of precursors to pyridoxal-5-phosphate under optimal conditions. To examine this apparently paradoxical phenomenon, we have concentrated our efforts for the past three years on development of methods to examine B6 and glycogen metabolism in detail in isolated subpopulations of both developing and mature blood cells, and in numerous other tissues (particularly lymph nodes, liver, spleen, and muscle).

During the past year, we have concentrated primarily on isolating subpopulations of blood cell precursors from the bone marrow. The technique which appears to suit our needs most satisfactorily so far uses velocity sedimentation at unit velocity.^{1,2} In this technique, bone marrow cells (or cells from another tissue, such as spleen, tonsil, or lymph node) are disaggregated, washed, and centrifuged at less than 4000 x g for 10 minutes, and

resuspended in phosphate buffered saline (PBS) with 0.3% bovine serum albumin (BSA). Cell counts are adjusted to 5×10^5 /ml in order to prevent streaming on the separation column. A Sta-Put Cell Separator (Johns Scientific, Toronto) is employed, with its gradient generator system loaded with 600 ml Minimal Essential Medium (MEM) and 1% BSA in Bottle A, and 600 ml MEM with 2% BSA in Bottle B. The top layer of 50 ml PBS with 0.3% BSA is first loaded into the column, followed by the previously prepared cell charge. A buffer gradient of 0.5% BSA in MEM is then introduced. After all air bubbles are removed, all clamps from the gradient generator bottles are opened, and the separator chamber is allowed to fill, lifting the cell layer off the bottom. After all the BSA solutions are instilled, sedimentation is permitted to continue for an additional 3.5 to 4 hours. The column is then drained, discarding the cone volume, in fractions of 30 ml. Each fraction or pair of fractions is pooled, and then each pooled fraction is centrifuged and resuspended in a total volume of 500 μ l fetal calf serum and plated on slides for later histologic studies. The remainder of each pooled fraction is lysed with ultrasound, and biochemical studies are performed on the lysate.

Other separation techniques, particularly elutriation, centrifugation with PVP beads, and fluorescent activated cell sorting, will also be examined and compared to velocity sedimentation. Centrifugation with a Ficoll-Hypaque density gradient was shown not to be adequate for separation of bone marrow precursors, in a series of studies in our laboratory last year.

Progress and Results

1. Pilot studies (completed during FY 75) and other studies to define any gross abnormalities in B6 metabolism in Hodgkin's patients

Our pilot studies on this protocol, performed in FY 75, indicated that some but not all patients with Hodgkin's disease or other malignancies have lower plasma B6 levels than control subjects, and increased capability for red cell conversion of precursors to pyridoxal-5-phosphate under optimal conditions. Subsequent studies in our laboratory confirm our earlier observations, but indicate that, among hematologic malignancies, there is a spectrum of alterations in B6 metabolism. In our initial studies, we also found that patients with infectious mononucleosis have enzyme and PLP levels intermediate between those of patients with malignancies and controls. PLP levels per cell are not abnormal in either the RBC's or the lymphocytes, and the red cell levels appear to reflect the plasma levels.

2. Results of current efforts

Subpopulations of bone marrow erythroid precursors have been successfully separated by unit gravity sedimentation. These subpopulations are being examined in detail with regard to their metabolism of B6, glycogen, and purines.

3. Planned studies during the next fiscal year

A particularly promising technique which will allow us to approach more directly the analysis of B6 metabolism in Hodgkin's Disease is the use of isokinetic gradients to separate different types of cells from splenic, tonsillar, or lymph node tissue.³⁻⁹ One fraction which can be readily isolated by this technique is the one containing mononucleated Hodgkins cells and Reed-Sternberg cells.¹⁰

Conclusions: None

Funds Utilized, FY 78: None

Funds Requested, FY 79: None

Publications, FY 79: None

Type of Report: Interim

References:

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4. Pretlow, T.G. II, and Boone C.W. Separation of mammalian cells using programmed gradient sedimentation. *Exp Mol Pathol* 11:139, 1969
5. Pretlow, T.G. Estimation of experimental conditions that permit cell separations by velocity sedimentation isokinetic gradients of Ficoll in tissue culture medium. *Anal Biochem* 41:248, 1971
6. Pretlow T.G. II, Weir, E.E. and Zettergren, J.F. Problems connected with the separation of different kinds of cells, in Epstein MA, Richter GW (eds): *International Review of Experimental Pathology*, vol 14. New York, Academic, 1975, p91
7. Pretlow, TG II, and Luberoff, D.E. A new method for separating lymphocytes and granulocytes from human peripheral blood using programmed gradient sedimentation in an isokinetic gradient. *Immunology* 24:85, 1973
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Work Unit No.: 9010

Title of Project: Vitamin B6 Metabolism in the Hematopoietic System of Patients Receiving Isoniazid and Patients with Sideroblastic Anemia

Investigators:

Principal: LTC John A. Kark, MD MC

Associate: LTC Michael J. Haut, MD MC

Objectives: To determine whether further knowledge of the alterations of vitamin B6 metabolism due to (1) isoniazid and (2) sideroblastic anemia would improve the diagnosis and management of complications.

Technical Approach: New methods for measuring all 6 forms of vitamin B6 in biological tissues are being studied in our laboratory. These methods include high performance liquid chromatography and thin layer chromatography.

Progress and Results: No new results have been obtained, pending the development of better technical methods.

Conclusions: No new conclusions have been reached, pending the application of new methods.

Funds Utilized, FY-78: None

Funding Requested, FY-79: None

Publications, FY-78: Manuscripts in preparation

Type of Report: Interim

Work Unit No: 9012

Title of Project: The Effect of Infectious Hepatitis on Erythroid Colony Formation in the Plasma Clot Culture Method.

Investigators:

Principal: MAJ August Salvado, MD MC

Associate: MAJ William Butler, MD MC
Nancy Josza
LTC Jeffrey Berenberg, MD MC

Objectives: To determine whether the hepatitis virus which can cause abnormalities in all three cell lines in the injury in the stem cell population of the bone marrow.

Technical Approach: The plasma clot tissue culture technique for hematopoietic stem cells is used to determine colony growth of committed erythroid stem cells from the marrow of patients infected with hepatitis. "Normal" control marrow is obtained as an extra aspirate from patients having bone marrow aspirates done as a staging workup for other malignancies & whose marrow ultimately shows no evidence of invasion by malignant cells.

Progress & Results: Delay is still being encountered in the acquisition of patients for the study. The techniques of the plasma clot culture system are now fully developed to show human erythroid stem cells and as a matter of fact we have now cultured 7-10 marrows from patients who would qualify as controls for the study. Our studies with these individuals show 100-250 CFUE or late erythroid stem cells/ 10^5 nucleated marrow cells plated and 30-80 BFU-E or early erythroid stem cells/ 10^5 nucleated marrow cells plated. These figures agree quite well with those in the literature. We will continue to acquire such control data as patients become available and with the recently acquired cooperation of Dr William Butler and Dr. Jeffrey Berenberg who have agreed to help us on this study, we believe we will have much more success in locating hepatitis patients who qualify for the study.

Conclusions: Not applicable

Funds Utilized FY-78: None

Funding Requirements FY-79: None

Publications: None

Type of Report: Interim

Work Unit No: 9013

Title of Project: The Carbohydrate Dependence of Platelet Surface Interactions in Hypercoagulable States

Investigators:

Principal: MAJ Salvatore Scialla, MD MC

Associate: LTC Michael J. Haut, MD
MAJ Grant Taylor, MD MC
LTC Jeffrey Berenberg, MD MC

Objectives: To examine platelets and plasma from selected individuals with hypercoagulable states to determine if altered carbohydrate and/or carbohydrate synthesizing capacity is present.

Technical Approach:

1. Platelets and plasma are separated from blood drawn from controls and cancer patients.
2. Coagulation profiles are performed on the plasma sample which includes a detailed analysis of Factor VIII complex.
3. Detailed analysis of the Factor VIII complex includes a separation procedure by chromatography using agarose. Sialic Acid content of Factor VIII is determined by the Warren Method.
4. Platelet surface sialyltransferase is determined by a C¹⁴ Sialic Acid incorporation assay with platelets as the enzyme source.
5. Platelet surface sialic acid is determined by incubation with neuraminidase and subsequently the sialic acid assay by Warren.
6. The above studies are correlated with platelet aggregation by a photometric method.

Progress and Results: A pilot study has demonstrated that our group of cancer patients has accelerated coagulation, increased factor VIII antigen and Ristocetin cofactor, and enhanced ADP induced platelet aggregation platelet exogenous sialyltransferase activity was significantly increased in the cancer patients. Our work this year is to clarify the mechanism of sialyltransferase activity and platelet function. Also we are studying the interaction of platelet function and factor VIII sialic acid content.

Conclusions: A group of cancer patients clinically prone to thrombosis demonstrated greater platelet aggregation and platelet sialyltransferase activity than normal controls.

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications: Abstract Blood 50:282, 1977

Manuscript submitted to Cancer Research

Type of Report: Interim

Work Unit No.: 9014

Title of Project: Dengue Fever Virus and Human Monocyte Interactions

Investigators:

Principal: MAJ Carlos C. Daughaday, MD MC

Associate: Walter Brandt, PhD

Objectives: The human monocytes has been identified as the cell in which Dengue fever virus replicates in vivo and in vitro. The mechanisms which make monocytes permissive to virus replication are believed to be controlled by the receptors for virus on the surface of cell. Other work has indicated that immune IgG complexed with the monocyte Fc receptor serves as the virus reception and is responsible for enhanced viral replication in vitro. The objectives of this project are to characterize the relationship of Dengue fever virus replication in cultures of human monocytes to virus specific antisera and the status of the Fc receptor.

Technical Procedures: Blood is obtained by venipuncture from normal human volunteers and mononuclear cells separated using conventional Ficoll Hypaque gradient centrifugation. The monocytes are further purified by plastic adherence. standard quantities of dengue fever virus are added to the cultures in the presence of immune on normal serum and samples are removed daily to assay plaque forming units. In some experiments the monocyte monolayers are pretreated with trypsin prior to inoculation in order to digest nonspecific adhering to the monocytes. The role of the Fc receptor was investigated by culturing virus inoculated monolayers in the presence of F(ab)₂ fragments of immune IgG (prepared by Pepsin digestion) and commercial anti human Fab.

Progress and Results: During the past two years we have successfully prepared F(ab)₂ fragments from both normal and Dengue immune serum. The identity of the fragments was confirmed by Ouchterlong immunodiffusions and the viral neutralization titer was 1:60. Earlier experiments had shown that viral replication did not occur in monocyte cultures from nonimmune donors unless small amounts of immune serum was added. However, occasionally replication was observed in normal monocytes. It was found that brief treatment of the monocyte monolayers with trypsin prevented replication in the presence of normal serum and optimized the enhancing effect of immune serum. These results suggest that small amounts of nonspecific antibody adherent to the monocyte Fc

receptors are providing a receptor for the virus. Addition of F(ab)₂ fragments of immune serum did not restore replication. If the Fc receptor and the Fc portion of IgG are required for viral entry and replication into monocytes, one would expect that replication could be restored by using a sandwich technique to bind the F(ab)₂ fragments to the receptor. We propose to test this prediction by adding F(ab)₂ fragments of immune IgG prepared in our laboratory and commercially available anti human Fab.

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications, FY-78: None

Type of Report: Interim

Work Unit No: 9015

Title of Project: The Effect of Pyridoxine on Red Cell Metabolism
of B6 and on the Oxygen-Affinity of Hemoglobin

Investigators:

Principal: LTC John A. Kark, MD MC

Associate: LTC Michael J. Haut, MD MC

Objectives: To determine changes in plasma and red cell vitamin B6 metabolism and in the oxygen-affinity of hemoglobin in normal subjects who take pharmacologic doses of pyridoxine.

Technical Approach: Measurements will be made of plasma and erythrocyte levels of B6 compounds, activities of erythrocyte enzymes involved in B6 metabolism, and oxygen-dissociation curves for intact erythrocytes, as outlined in the original application.

Progress & Results: This protocol has not been active, pending the completion of modifications to the volunteer agreement, which have been recently submitted.

Conclusions: None

Funds Utilized, FY-78: None

Funding Requested, FY-79: None

Publications, FY-78: None

Type of Report: Interim

Work Unit No: 9016

Title of Project: Investigation of Pyridoxine as a Treatment for Sickle Hemoglobinopathies.

Investigators:

Principal: LTC John A Kark, MD, MC

Associate: MAJ Milton P. Kale, MD, MC
CPT Peter G. Tarassoff, MD, MC
Lawrence S. Lessin, MD

Objectives: To determine whether one of the B₆ vitamins can be used for non-toxic prophylactic treatment to prevent the pathologic effects of HbS, including sickle trait.

Technical Approach:

1. Pyridoxine at 30 μ M concentration was found to have a small antisickling effect under restricted conditions. Further investigations are being carried out to define the mechanism of this antisickling effect. Cells from normal individuals are being incubated with pyridoxine, varying the type of suspending medium and the length of incubation to determine how this membrane-mediated effect occurs.

2. Pyridoxal at 1 to 20 μ M concentration was found to have a profound antisickling effect. Sickle cells treated with pyridoxal were incubated and fixed under low oxygen. Morphologic studies demonstrated profound inhibition of sickling. Measurements of oxygen affinity by tonometry and by use of the Guinico-Bowman oxygen association curve analyzer (the "Hem-O-Scan") demonstrated that most of this effect can be explained by stabilization of oxyHb, i.e. by greatly increased oxygen affinity of modified Hb. Modification of Hb by pyridoxal has been examined by iso-electric focusing and now is being further characterized by absorption and fluorescence spectra on peptide digests of isolated hemoglobin.

Conclusions:

1. A small but consistent antisickling effect of pyridoxine was confirmed since studies in FY-77, and the restricted conditions necessary to demonstrate this effect were defined. These conditions could be relevant to the production of sickle crisis. Therefore, further investigation of the mechanism, to obtain an idea of clinical relevance is indicated.

2. Pyridoxal has a profound antisickling activity, probably greater than that of cyanate. This activity is probably due to the great increase in oxygen affinity of pyridoxal-HbS. At present pyridoxal appears to be the least toxic agent for use as an extracorporeal carbamylating agent in the treatment of sickling hemoglobinopathies.

Funds Utilized FY-78: None

Funding Requested, FY 79: None

Publications:

JA Kark, MP Kale, RG Tarasoff, M Woods, and LS Lessin: Inhibition of erythrocyte sickling in vitro by pyridoxal. The Journal of Clinical Investigation 62:888-891, October, 1978.

Type of Report: Interim

(The initial studies are extremely promising, and further work is in progress to define the properties of the observed antisickling effects).

Work Unit No: 9017

Title: Treatment of Sickle Cell Anemia with Pyridoxine

Investigators:

Principal: LTC John A. Kark, MD MC

Associate: MAJ Milton P. Kale, MD MC
Lawrence S. Lessin, MD

Objectives: To determine whether ingestion of pyridoxine can reduce signs of in vivo sickling of erythrocytes in patients with sickle cell anemia.

Technical Approach: Levels of plasma and erythrocyte PLP, blood ISC's, rate of in vitro sickling under standard conditions, and the mean red cell life span will be measured before, during, and after administration of pyridoxine.

Progress & Results: This protocol has not been active pending approval by the Human Investigation Board of George Washington University Medical Center, which was obtained and submitted, and alterations in the volunteer agreement, which were submitted recently.

Recently demonstration of a more potent effect of the related form of vitamin B6, pyridoxal, might lead to an additional arm of this study, using pyridoxal instead of pyridoxine.

Conclusions: None

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications, FY-78: None

Type of Report: Interim

Work Unit No.: 9018

Title of Project: De Novo Synthesis of Purine Nucleotides in Human Erythrocyte Precursors.

Investigators: LTC Michael J. Haut, M.D., MC
John Prichard, M.S. (GS-11)
LTC Robert H. Prall, M.D., MC
MAJ August J. Salvado, M.D., MC
CPT H. Kyle Webster, Ph.D., MSC

Objectives: We propose to study purine synthetic capability in human blood cells, specifically the reticulocyte and members of the erythroblast series. Initially, levels of adenylosuccinate synthetase will be measured in both reticulocytes and bone marrow fractions. Enzymes utilized earlier in the pathway will be assayed subsequently.

Technical Approach:

A. Enzyme Assays:

1. Adenylosuccinate synthetase: We have established in our laboratory a previously-published micromethod in which IMP and aspartic acid are permitted to react in the presence of magnesium ion and a regenerative GTP source. In the presence of adenylosuccinate synthetase (AS-synthetase), the system generates adenylosuccinate. In reaction mixtures in which the enzyme source includes AS-lyase, some production of AMP would be anticipated. The activity of AS-synthetase is therefore determined by the increase in AS concentration, and, if present, the increase in AMP concentration. ^{14}C -IMP is used as the substrate. Thin-layer chromatography using PEI plates and a formate gradient solvent phase is employed to separate IMP and AMP from AS. Cut-out spots are subjected to scintillation counting for quantitation of the reactant and product(s).
2. Incorporation of glycine and formate into purines: Enzymes earlier in the sequence will be assayed using a basic incubation system employing ^{14}C -formate and ^{14}C -glycine, in association with thin-layer chromatography and liquid scintillation counting.

B. Enzyme Sources:

1. Rabbit muscle (for methods development): The rabbit muscle used to develop our assays is obtained as frozen muscle from the Pel-Freeze Company.
2. Human Reticulocytes: Human reticulocytes are obtained from patients with high reticulocytosis. We have been able to get solutions containing only reticulocytes and mature red blood cells by passing freshly drawn blood through a syringe filled

2. Measurement of AdSS activity in erythroid precursors: experiments were performed to identify the number of cells necessary to render AdSS activity detectable by our assay technique. A series of human marrow cell suspensions was prepared from 3×10^5 to 3×10^8 cells per ml in 10-fold increments. Results of one such experiment are summarized in Table I.

Cell Concentration	Average Reaction Rate	
Negative control	0	cpm/m
3×10^5 per mL	0	cpm/m
3×10^6 per mL	0	cpm/m
3×10^7 per mL	3.8	cpm/m (NS)
3×10^8 per mL	19.2	cpm/m

TABLE I

The average reaction rate of 3.8 cpm/m achieved by 3×10^7 cells per mL is not statistically significant. A rate of 19.2 cpm/m obtained with 3×10^8 cells per mL is highly significant, however, and represents the first demonstration of AdSS activity in human bone marrow cells. Technical problems apparent in this procedure indicated that the efficiency of a assay was still relatively low.

Additional studies were performed in which human whole marrow was assayed for adenylosuccinate synthetase, in concert with positive and negative controls. In addition, an attempt was made to demonstrate activity enrichment after elimination of erythrocytes and mature granulocytes by Ficoll-Hypaque cell separation. Results are summarized in Table II, for whole marrow.

Product	0'	15'	30'	45'	Average
AdSA	269	468	678	898	13.9 cpm/m
AMP	113	171	240	324	4.7 cpm/m

TABLE II

Production of AdSA at a rate of 13.9 cpm/m is statistically significant by the criteria mentioned previously, as is the production of AMP at a rate of 4.7 cpm/m. However, no discernable reaction rate for the production of either compound was obtained after Ficoll-Hypaque separation. Before and after cell counts disclosed that only half the cells loaded into the Ficoll-Hypaque system are retrieved, making its efficiency extremely low. Therefore, a series of interim procedures were conducted in which the dependence of chromatographic separation of pH was explored. We found an absolute requirement for close control of the pH at which the products are applied to the plates. Below pH 5.5 or above 7.5, the migratory behavior of these nucleotides is erratic, despite the fact the pH of the solvent is 3.6. Our sonication procedure was improved to yield virtually complete cytolysis. Another experiment was conducted after these factors were controlled, in which we assayed both whole marrow, and marrow subjected to Ficoll-Hypaque separation. Results for whole marrow, for the cells at the interface, and for the cells in the pellet are presented in Table III.

Product	0'	15'	30'	45'	Average
AdSA-marrow	514	1848	3713	4986	99.4 cpm/m
AdSA-inter-face	481	1412	2263	3352	63.8 cpm/m
AdSA-pellet	416	1094	1666	2143	38.3 cpm/m
AMP-marrow	123	601	980	1319	26.6 cpm/m
AMP-inter-face	132	226	277	289	3.5 cpm/m (NS)
AMP-pellet	143	171	174	174	0.7 cpm/m (NS)

TABLE III

In whole marrow, a reaction rate of 99.4 cpm/m was obtained for the production of AdSA, which represents a substantial improvement in the efficiency of the assay. After Ficoll-Hypaque separation, a reaction rate of 63.8 cpm/m was obtained from the cells at the interface, and 38.3 from the the cells in the pellet. When corrected for a cell loss factor of 50%, these reaction rates indicate Ficoll-Hypaque partitioning of AdSS activity by approximately 25%. While these figures achieve high statistical significance relative to duplicate variation, the small amount of enrichment by cell separation is more than offset by cell loss factors.

with equal weights of alpha cellulose and microcrystalline cellulose. Demonstration of activity of a particular enzyme in this combination of cells, and demonstration of the lack of the enzyme in purified mature erythrocytes, would suggest that activity of that particular enzyme is lost as the reticulocyte matures.

3. Human Bone Marrow: Human bone marrow specimens are obtained from ribs in those patients undergoing rib resection for thoracotomy (see Human Use section below). These specimens are additionally subjected to Ficoll/Hypaque density-gradient fractionation and/or velocity sedimentation at unit gravity in order to obtain well-resolved cell-type fractions. In the Ficoll/Hypaque technique, separation of mature erythrocytes and granulocytes from nucleated precursors and monocytes is achieved. A suspension of cells derived from human marrow is mixed with Ficoll and Hypaque, and centrifuged at 400 g. A band of cells develops at the interface between the Ficoll and the Hypaque, containing a preponderance of nucleated cells. A pellet of cells develops at the bottom of the tube consisting predominantly of mature red cells and granulocytes. These are harvested separately, lysed with ultrasound and centrifuged. Enzyme activity of the supernatant is measured. In the velocity sedimentation procedure, cells are fractionated according to sedimentation rate at unit gravity. A suspension of bone marrow cells is introduced into a chamber along a gradient of fetal calf serum. Sedimentation is permitted to occur in a vibration-free, cold environment, after which the fluid column is examined histologically, and lysed with ultrasound. Enzyme activity is then measured in the supernatant.

Progress & Results:

1. Development of methodology specific for the project.
 - a. Isolation of erythrocyte precursors: Isolation of reticulocytes was accomplished by passing whole blood through syringes containing a mixture of alpha cellulose and microcrystalline cellulose. In one patient with a peripheral reticulocyte count of 27%, a reticulocyte stain of the cell mixture passing through this "mini-column" showed 27% reticulocytes and 73% mature erythrocytes.
 - b. Isolation of bone marrow erythroid precursors: Human rib bone marrow obtained at operation was separated by velocity sedimentation into 18 discrete fractions, which showed enrichment of several specific fractions with erythroid precursors of different mean ages. Only a small number of the fractions contained the majority of the precursors.

Tables II and III have also presented reaction rates for the production of AMP. The fact that AMP is produced in any quantity indicates the presence of AdSL, at least in whole marrow preparations. Theoretically, since every count in AMP ought to have come from AdSA, AMP counts could be added to those in AdSA and would serve to increase the apparent reaction rates and thus the estimate of AdSS activity. Since such a manipulation of the data is not necessary to establish the presence of AdSS in this tissue, and since the inclusion of AMP counts raises a number of additional questions, the increase in AMP counts was ignored.

Histologic examination of the cell fractions generated by Ficoll-Hypaque was performed. As suggested by the 1.5:1 ratio of counts between interface and pellet cells, the technique does not achieve a definitive separation of nucleated cells, but rather only a slight enriching effect. Despite this small effect, the technique may have some preparative value if cell loss factors can be reduced.

3. Demonstration of de novo incorporation of glycine or formate into purines: A small but significant incorporation of labeled glycine and formate into purines was shown in whole marrow. Since this pathway is easier to demonstrate in rapidly growing cells, future studies will include erythropoietin in the assay medium, and may even include a preincubation step. By preincubating the marrow with erythropoietin and by utilizing several recent improvements we have made in our cell lysis and enzyme assay techniques, we should be able to examine de novo incorporation of glycine and formate in isolated erythroid cells definitively in the near future.

Conclusions: So far, we can conclude that adenylosuccinate synthetase activity and de novo incorporation of glycine and formate into purines are present in whole marrow. During the coming year, we should be able to demonstrate the presence or absence of the above synthetic activities in isolated erythroblasts.

Funds Utilized, FY-78: None

Funds Requested, FY-79: None

Publications, FY-78: None

Type of Report: Interim

Project No.: 9025

Title of Protocol: Functional Characterization of Human Intestinal Lymphocytes in Gastrointestinal Disorders.

Principal Investigator: Robert H. Reid, MAJ MC, Chief, Immunology Section

Dept of Gastroenterology, WRAIR

Sixteen subjects were studied in 1977 and four in 1978, all without complications. This preliminary work has led to the following collaborative results which have been published as an abstract (1).

Cytotoxic lymphocytes may mediate inflammatory bowel disease (IBD) but have not been demonstrated in normal or IBD intestinal mucosa. Therefore we have examined human intestinal mucosa for the presence of cytotoxic lymphocytes using a sequential dithiothreitol-EDTA-collagenase technique, we examined lymphocytes obtained from mucosa of 18 normal (uninvolved tissue from colon cancer patients) human colons and 14 colons involved with IBD, all obtained at surgery. The percentage of specimens with cytotoxic cells was as follows:

Assay	Targets	Normal		IBD	
		Unsep	moDepl	Unsep	moDepl
ADCC	Chick RBC	83%	83%	100%	100%
	Chang Line	20%	20%	30%	33%
SCMC	K562 Line	38%	33%	17%	0%
	Chang Line	31%	20%	25%	0%
LICC	Human RBC	81%	100%	91%	67%

ADCC and LICC activity persisted but SCMC decreased following G-10 macrophage depletion. No striking difference in cytotoxic capability was noted between normal and IBD intestinal cells. Surface characteristics revealed 35.5 ± 5.2 (mean \pm S.E.M.) E rosetting, 6.6 ± 1.6 EA rosetting, 13.8 ± 2.8 SIg positive, and 10.8 ± 1.6 esterase positive cells. No difference in surface characteristics between unseparated IBD and normal intestinal mucosal mononuclear cells was noted. These experiments demonstrate: 1) Fc-receptor bearing lymphocytes as well as T and B cells and macrophages are present in normal and IBD human intestinal mucosa. 2) Lymphocytes from both normal and IBD human intestinal mucosa mediate ADCC and LICC with red cells as targets. 3) Intestinal mononuclear cells occasionally mediate ADCC and SCMC with cell lines as targets. 4) No major difference in cytotoxic capabilities or surface characteristics between normal and IBD intestinal lymphocytes has been observed.

Since no major differences were found in the lamina propria lymphocytes from normals and patients with IBD, the cellular regulation of their immunological responsiveness may be important.

Interaction between gut associated lymphoid tissue (GALT) and systemic lymphocytes may be important in the local regulation of the intensity of the host immune response to foreign antigens. We investigated the ability of the rabbit ileal lamina propria (LP) mononuclear cells (lymphocytes and macrophages) isolated by collagenase digestion to influence the autologous

splenic lymphocyte response to PHA. Thymidine ^3H uptake by 3×10^5 splenic lymphocytes in replicate microcultures was inhibited approximately 25, 50 and 75% by the addition of 0.3, 0.75 and 1.5×10^7 LP cells respectively in repetitive experiments. The suppression cannot be attributed to PHA binding by the LP cells since experiments which maintained the total cell population constant (by reducing the splenic cells 5, 10 and 25% and adding back equal numbers of LP cells) also produced inhibition at 15, 20 and 90% respectively in repetitive experiments. The suppression is blocked 50-100% by irradiating the LP cells with the macrophage sparing dose of 6,000 R. This suggests that the suppression is an effect of the LP lymphocytes. The above experiments were performed in normal adult New Zealand white rabbits. A similar suppression was seen using LP cells isolated from animals which had been hyperimmunized with foreign proteins via a chronic ileal (Thiry-Vella) loop. However, suppression of splenic lymphocytes was not seen using LP cells isolated from germ free animals which had been reassociated with a defined, but limited, enteric flora. These latter observations suggest a relationship of the suppressor effect to the degree of intestinal immunization. Suppression was not seen if Peyer's patch or mesenteric lymph node cells replaced the LP cells. These data demonstrate suppression of the splenic lymphocyte PHA response by the LP mononuclear cells and suggest that the LP cells might prevent the systemic T lymphocytes from participating in an immune mediated inflammatory response in the intestine of the normal rabbit. These results are published as an abstract (2).

A temporary technician was hired from 28 Dec 1977 to 30 July 1978 to support the above work. The technician was trained to do surface characteristic determinations and helped develop the animal model. This technician also carried-out the surface characteristic determinations on Dr. Sjogren's protocol and a collaborative study with the University of Kentucky. Dr. Sjogren studied nine patients and thirteen normals all without complications. This study gave the following results which have been written into a paper to be submitted for publication (3).

It has been proposed that cimetidine may adversely enhance cellular immune function in patients being treated for duodenal ulcer disease. We therefore studied nine patients with duodenal ulcer disease immediately prior to, after 2-3 weeks and after 6-8 weeks of cimetidine treatment. There were thirteen normal controls not taking cimetidine. Whole blood cimetidine and serum immunoglobulin levels (IgG, IgA, and IgM) were determined. Peripheral blood lymphocytes obtained by ficoll hypaque separation were analyzed as to their surface characteristics, cytotoxic capabilities, and responsiveness to mitogens. Cytotoxic and mitogenic assays were performed in paired media, one containing the subject's own serum drawn simultaneously with the cells and the other containing fetal calf serum. Therapeutic blood levels of cimetidine were present in all patients at the time of assays. Total white blood cell and mononuclear cell counts did not change in the interval studied. Although patient's granulocyte counts, which were moderately elevated before cimetidine therapy, fell to within the normal range by 68 weeks of therapy, no patient became granulocytopenic. Surface characteristics (percent cells esterase positive; surface immunoglobulin positive;

E rosette; EA rosette; and EAC rosette forming) did not change during the treatment period. The ability of peripheral blood cells to mediate spontaneous cell mediated cytotoxicity of K-562 cells was markedly impaired in duodenal ulcer patients prior to treatment and returned to normal after 2-3 weeks of treatment. The capacity of patient's peripheral blood cells to mediate antibody dependent cellular cytotoxicity to either chick RBC or K-562 cell line cells, or lectin induced cellular cytotoxicity to human RBC was not altered by cimetidine during the course of therapy. Likewise, mitogenic responsiveness to PHA, Con A. and PWM remained unchanged in patients while treatment with cimetidine was being given. Furthermore, there were no difference in any of the results between assays run in the patients own serum from that day in comparison to fetal calf serum. Finally, serum immunoglobulin levels did not change during cimetidine treatment. We conclude cimetidine therapy in vivo for up to eight weeks induces no marked enhancement or alteration of general cellular immune function.

The collaborative study with the University of Kentucky had the following results which have been written into a paper to be submitted for publication (4).

No consistent functional immunologic defect has been found in our studies of the mitogenic responses and cytotoxic abilities of peripheral blood lymphocytes from three patients with Whipple's disease. One patient was studied both during active disease and after therapy, whereas the other two were studied only after therapy. All three patients had a decreased percentage of peripheral blood T lymphocytes; however, their mitogenic responses to phytohemagglutinin, concanavalin A and pokeweed mitogen were usually as vigorous as those of concurrently examined normal subjects. In addition, all three patients were able to produce cutaneous hypersensitivity responses. Likewise, cells from these patients usually produced antibody-dependent cell-mediated cytotoxicity at control levels, but spontaneous cell-mediated cytotoxicity was decreased in two convalescent patients. No serum inhibitor could be demonstrated in those instances where patient mitogenicity cytotoxic responses were lower than those of controls. The present study indicates that if an immunologic defect exists in patients with Whipple's disease, its expression is not as broad or clearly delineated as earlier studies have suggested. More detailed longitudinal studies of immunologic functions in patients with Whipple's disease may help to clarify the nature of immunologic responses in these individuals.

Dr. Summer Kraft, Professor of Medicine and Immunology, the University of Chicago is an authority on inflammatory bowel disease. Beginning 1 July 1979, he will be spending a year's sabbatical leave on active duty in our laboratory. He may want to be an investigator on this protocol at that time.

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Work Unit No: 9027

Title: Relationship of Vital Signs to Cardiac/Respiratory Arrest

Date: 25 January 1978

Investigators: Principal: Madeline L. Bluemle, LTC, ANC
Associate: Elenore F. Sullivan, COL, ANC

Objective: To identify and describe relationships of vital signs during the six hours preceding cardiac or respiratory arrest, as possible indicators of impending arrest.

Technical Approach: Review of charts of patients, age one and over who were identified as having had cardiac or respiratory arrest at Walter Reed Army Medical Center from January 1975 to January 1977. Cardiac or respiratory arrest had either to be diagnosed as such in the patient record, or had to meet the definition of having a sudden, abrupt onset of cessation of cardiac or respiratory activity. Temperature, pulse, respiration, and blood pressure were examined, for periods of six and 24 hours preceding arrest, in terms of total variation; interrelationships; relationships to age, sex, and type of arrest; and changes in descriptive characteristics of respiratory and circulatory measurements. If a patient had more than one arrest, each was treated as a discrete event. Data analysis was limited to descriptive statistics.

Progress & Results: Charts of 66 patients who experienced 88 arrests were examined. Forty-three males had 73% of arrests; 23 females had 27%. Age ranged from 2-98 years, with a median of 53. Fifty-four patients had only one arrest; 12 patients had from 2-5 arrests. Cardiac arrests accounted for 68% of arrests, respiratory for 10%, and mixed (e.g., respiratory → cardiac) in the remaining 22%. Diagnoses of all but 7 patients were multiple, but over 70% of primary diagnoses were referable to the gastrointestinal, pulmonary, or cardiovascular systems. Complications prior to arrest were seen in the majority of patients, ranging from 0-7, with a mode of 3. Medications capable of affecting one or more vital signs were in use prior to all arrests, ranging from 1-12 per arrest, with an average of 5.7 and a mode of 4. Antihypotensive drugs were in use prior to 40 arrests, antihypertensive prior to 7 arrests.

Preliminary data collection revealed paucity of vital sign measurements during the 6-hour period pre-arrest in many cases. The data collection period was therefore extended to 24 hours pre-arrest. Preliminary analysis of data of 30 arrests, done to evaluate pulse pressure as a possible indicator of impending arrest, showed this method to be unfruitful. In its place, cumulative, or total variation in systolic and diastolic blood pressure, as well as other vital signs were calculated and appeared indicative of failure of compensatory hemodynamic responses. This, then, became the method for calculating change in vital signs.

Types and cumulative changes in vital signs during the 6 and 24 hours prior to arrest are presented in Tables 1 and 2. Cumulative decrease in systolic and diastolic pressure, as individual components of blood pressure, occurred in both time frames in the majority of arrests. Mean changes were large, when compared to mean changes of cumulatively increased pressure.

Cumulative decrease in total blood pressure, i.e., in both components of the same measurement, also occurred in the majority of arrests, but at lower percentages than for single components. If, however, incidence of cumulative decrease in total blood pressure is combined with its incidence in mixed blood pressure (i.e., decreased systolic or diastolic pressure with an increase or no change, or missing data in the other component), total incidence was 78% (61/88) during the 6-hour period and 76% (66/88) during the 24-hour period, a greater incidence than with either single component.

Lower percentages of blood pressure change in the 6-hour period could be indicative of lower blood pressures which had stabilized to some degree in response to either intrinsic factors or to intravenous antihypertensive drugs being administered, which occurred prior to 46% of arrests. Lower mean change during the 6-hour period tends to support this interpretation. Higher mean change of cumulatively increased diastolic pressure during the 6-hour period could indicate increase in peripheral vascular resistance, possibly in response to dopamine or Levophed administration.

Mean changes and ranges of cumulative increase of blood pressure, both as individual components or as total blood pressure, were smaller than cumulative decreased pressure. This could be indicative of a

weak compensatory response, or simply reflect arrests for which there are few or no predictive indices, at least in regard to vital signs. In mixed blood pressures, cumulative decrease in diastolic pressure also showed the lower variations in both time frames, while decrease in systolic pressure showed it in the 24-hour period. However, mean change of decreased systolic pressure in the mixed group was higher during the 6-hour period, which tends to indicate greater instability during this period.

Cumulative decrease in pulse rate occurred in the majority of arrests during both time frames, but in a higher percentage during the 6-hour period. However, mean change was higher during the 24-hour period. As with lower mean change in blood pressure during the 6-hour period, lower mean change in pulse rate could be indicative of a lower, but temporarily stable state. The higher percentage of arrests showing decreased pulse rate during the 6-hour period seemed to indicate greater instability in the total population with closeness to time of arrest.

Respiratory rate decreased in fewer than 50% of arrests in both time frames. However, respirations showed an increase in mean variation of decreased rate, as well as in percentage of arrests, during the 6-hour period, as compared with the 24-hour period. This also could be indicative of decreased capacity to respond appropriately to hemodynamic changes. It could be argued that, since patients were on respirators prior to 40 arrests, such changes during the 6-hour period could be attributed to changes in respirator control. However, recorded respiratory rates were quite variable and could not be correlated for most arrests with respiratory settings. It is quite possible that respirator settings were often adjusted but not recorded. In 55% of arrests of patients on respirators, respirations decreased during both time frames.

The range of increased respiratory rate variation during the 6-hour period was noticeably smaller than for the 24-hour period, or for decreased rate variation in either time frame. This could indicate either decreased responsiveness to hemodynamic changes, or less need for compensation based on sufficient oxygenation. Oxygen therapy was provided prior to 87% of arrests.

Temperatures cumulatively decreased in less than 40% of arrests and mean change was greater during the

6-hour period. The changes correlate with greater decreased pulse and respiration rates during the 6-hour period, with the exception of the higher mean change in decreased pulse during the 24-hour period.

Interrelationships of cumulative changes of vital signs were examined for each arrest. Those which did not show expected compensatory response, such as an increase of pulse rate with a decrease in blood pressure, were considered inappropriate responses. The summary presented in Figure 1 shows the cumulative variations in which blood pressure was falling (i.e., either systolic, diastolic, or both) without the expected rise in pulse rate and/or respiratory rate. Such inappropriate responses could be expected to result in decreased cardiac output, circulating volume, and respiratory exchange at both the alveolar and cellular levels, including the myocardium. Hypoxia, hypercapnia, acidosis, and arrhythmia could result and terminate in arrest. The blood pressure:pulse relationship appeared to be the most sensitive of the three relationships as an indicator of significant change.

Percentages of inappropriate responses increased with closeness to time of arrest in all groups. The greatest incidence of inappropriate change was noted in the blood pressure:pulse relationship. The increase of inappropriate response with closeness to time of arrest corresponds with the increase in percentage of decreased variation seen in the pulse rate (Table 2) from the 24 to the 6-hour period.

Percentages of arrests by age, sex, and type of arrest in which inappropriate vital sign responses occurred were compared with percentages in the total study population. Incidence of inappropriate blood pressure:pulse response by age was fairly similar to that of the total population. Incidence by type of arrest showed a much higher percentage of primarily cardiac arrest than in the total population. A noticeable difference from the total study population existed in regard to sex. In the total population, 73% of all arrests occurred in males, 27% in females. In arrests with inappropriate blood pressure:pulse response, 77% occurred during the 24-hour period and 75% during the 6-hour period pre-arrest in males. Percentages were 23 (24 hours) and 25 (6 hours) in females.

Incidence of inappropriate blood pressure:respiration response was generally similar to the total population except for age distribution. A much higher incidence occurred in the over age 65 category, the increase coming fairly equally from the other age groups.

When combined blood pressure, pulse, and respiration responses were examined, dissimilarities were found in percentages of age and type of arrest. A higher incidence in the over 65 group derived from all groups but mainly from the 40 to 64 age category. Incidence of this relationship during the 24-hour period pre-arrest was greatly increased in arrests which were primarily cardiac; percentage during the 6-hour pre-arrest period was similar to that of the total population. Increased incidence of cardiac arrest came from reductions in other types of arrest, but especially from that of primarily respiratory arrest. Forty percent (24 hours) and 44 percent (6 hours) of primarily cardiac arrests occurred in patients with some form of cardiovascular disease.

Certainly, decreased compensatory response with age is expected. Decreased appropriate response prior to primarily cardiac arrest could simply indicate the effectiveness of this type of monitoring. The decreased appropriate response in males is interesting and raises the question of whether males respond differently than females to this type of stress. This finding corresponds with shorter longevity seen in the male population in this country.

Arrhythmias occurred prior to 41% of arrests (36/88). These did not include simple rate changes such as tachycardia or bradycardia. There were 57 reported incidents, 29 during the 6-hour period and another 28 during the remaining 18 hours of the study period. Multiple ones occurred in 13 arrests. Because of imprecision in use of terms used to describe these arrhythmias, no attempt is made to report their characteristics. Of the 57 reported arrhythmias, 24 were associated with inappropriate vital sign responses in which there was a cumulative decrease in both blood pressure and pulse. In addition, 4 incidents of arrhythmias were associated with no cumulative increase in pulse rate when blood pressure cumulatively decreased. The 14 remaining arrhythmias showed no relationship to cumulative changes in vital signs.

Descriptive data concerning respiratory characteristics were scarce; in only 18 arrests (21%) were there comments concerned with respiratory function. In 12 of these arrests, comments concerned respiratory difficulty, mainly dyspnea. In 8 arrests, comments were concerned with actual description of respiratory rate, depth, or rhythm. Local or generalized cyanosis was reported in 21 arrests (24%).

Conclusion:

Cumulative variation in blood pressure and pulse seemed to provide data which could indicate impending cardiac or respiratory arrest. Monitoring of cumulative changes in temperature seemed of no value as a predictive tool. The value of monitoring of respiratory rate change was equivocal because of the effects of respiratory control of patients on respirators. However, retrospective data were very difficult to evaluate in this regard, thus, prospective data collection might result in a better evaluation of this parameter. Prospective studies should be conducted to further investigate the value of this simple methodology, cumulative variation, in predicting cardiac or respiratory arrest.

Other profitable studies might be concerned with respiratory compensatory response capability in older persons, the possibility of patients with impending arrest "over-riding" respirator settings, and incidence by sex of cardiac or respiratory arrest.

Type of Report:

Completed.

Table 1. Types and Cumulative Amounts of Change in Blood Pressure
6 and 24 Hours Prior to 88 Cardiac/Respiratory Arrests in 66 Patients.

Type of	Cumulative Change 6 Hours Pre-Arrest				Cumulative Change 24 Hours Pre-Arrest			
Change	# of Arr.	% of Arr.	Mean Change	Range.	# of Arr.	% of Arr.	Mean Change	Range
BP: Single Component:	N (S)=78		N (D)=74		N (S)=87		N (D)=85	
(-) S	56	72	47.2	2-130	63	72	51.7	2-160
(-) D	46	62	35.4	1-100	54	64	41.2	2-100
(+) S	17	22	11.5	2-36	22	25	15.6	1-56
(+) D	13	18	13.5	2-36	24	28	11.0	2-46
(o) S	5	6			2	2		
(o) D	15	20			7	8		
Total:	N = 78				N = 87			
(-)S/(-)D	41	53	$\frac{54.2}{38.4}$	$\frac{6-120}{1-100}$	51	59	$\frac{60.1}{42.6}$	$\frac{6-160}{2-100}$
(+)S/(+)D	7	9	$\frac{10.4}{14.6}$	$\frac{2-24}{6-30}$	14	16	$\frac{16.6}{12.0}$	$\frac{1-56}{2-46}$
(o)S/(o)D	2	3			1	1		
Mixed:	N = 78				N = 87			
With (-)S	15	19	$\frac{28.8}{-}$	$\frac{2-100}{-}$	12	14	$\frac{15.8}{-}$	$\frac{2-38}{-}$
With (-)D	5	6	$\frac{-}{11.2}$	$\frac{-}{8-18}$	3	4	$\frac{-}{14.7}$	$\frac{-}{10-20}$
With (+)S	10	13	$\frac{12.2}{-}$	$\frac{2-36}{-}$	8	9	$\frac{14.0}{-}$	$\frac{2-36}{-}$
With (+)D	6	8	$\frac{-}{12.3}$	$\frac{-}{2-36}$	10	12	$\frac{-}{8.3}$	$\frac{-}{2-20}$

(-) = Decrease (+) = Increase (o) = No change

Note: N is variable because all data were used, not just data
which included all four vital signs at one measurement.

Table 2. Types and Cumulative Amounts of Change in Pulse, Respirations, and Temperature 6 and 24 Hours Prior to 88 Cardiac/Respiratory Arrests in 66 Patients.

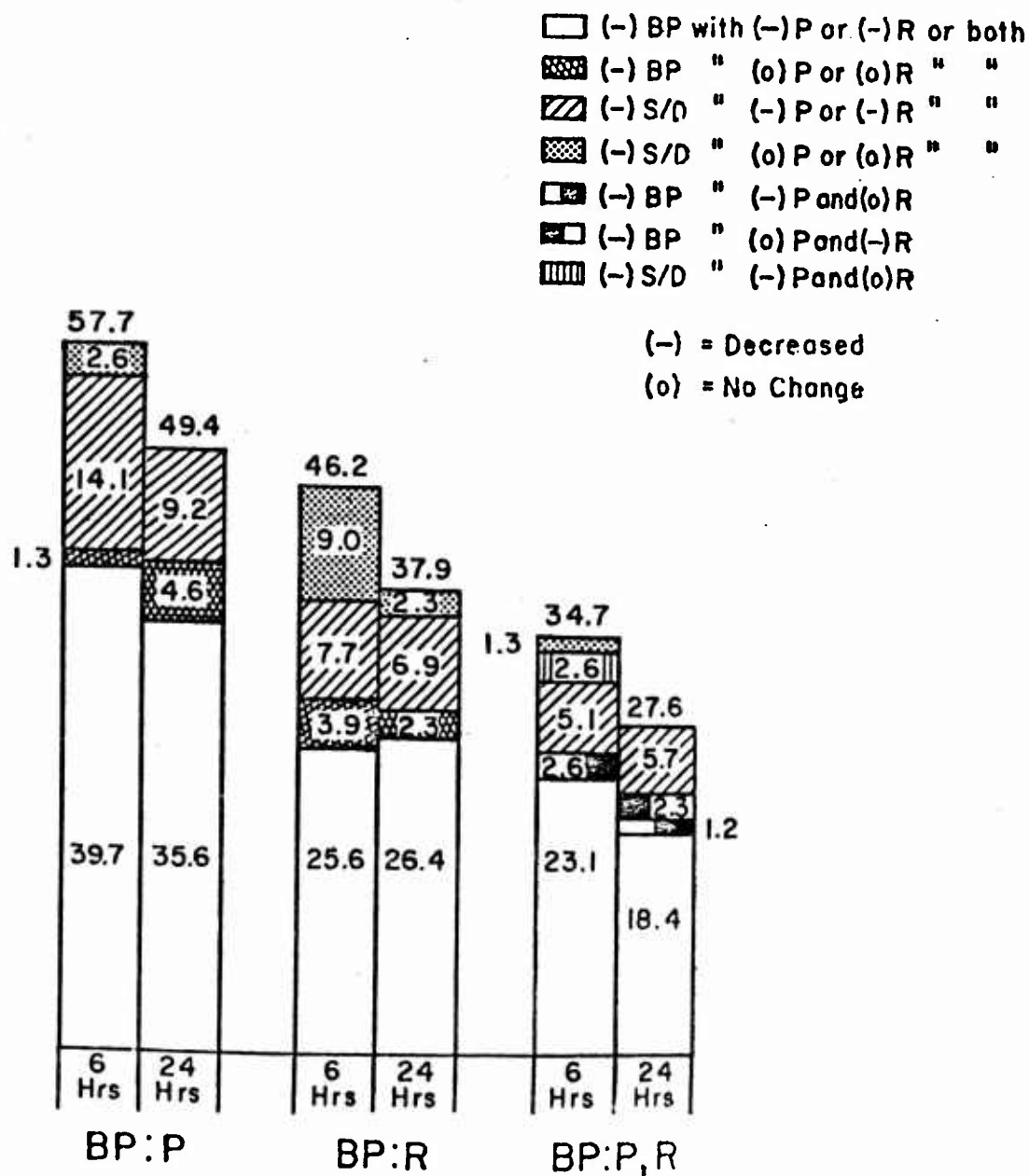
Type of Change	Cumulative Change 6 Hours Pre-Arrest				Cumulative Change 24 Hours Pre-Arrest			
	# of Arr.	% of Arr.	Mean Change	Range	# of Arr.	% of Arr.	Mean Change	Range
<u>PULSE:</u>	N = 80				N = 87			
(-)	54	68	50.8	2-140	50	58	55.9	2-140
(+)	22	28	19.9	2-56	30	35	20.3	2-56
(o)	4	5			7	8		
<u>RESP:</u>	N = 76				N = 86			
(-)	34	45	13.2	1-52	37	43	12.1	2-78
(+)	30	40	7.3	1-22	44	51	10.8	2-62
(o)	12	16			5	6		
(F) <u>TEMP:</u> (R)	N = 54				N = 87			
(-)	20	37	3.3	.2-6.7	32	37	2.1	.1-7.6
(+)	25	46	2.9	.1-7.6	50	58	1.9	.2-8.3
(o)	9	17			5	6		

(-) = Decrease (+) = Increase (o) = No change

Note: N is variable because all data were used, not just data which included all four vital signs at one measurement.

FIGURE 1.

PERCENTAGES OF INAPPROPRIATE CUMULATIVE VITAL SIGN CHANGES OCCURRING PRIOR TO 88 CARDIAC/ RESPIRATORY ARRESTS IN 66 PATIENTS



Final Progress Report
Clinical Investigation Program

Work Unit # 9031

The Effect of Prenatal Teaching on Breastfeeding

Submitted to: Clinical Investigation Committee
Thirty-First of August Nineteen-Hundred and Seventy Seven

Chief Investigator: Andrea Keene 1Lt./ANC
Associate Investigator: Betty Clifford LtComdr./NC
Assistant Investigators: Ann Paulen, Rita Baseman

TABLE OF CONTENTS

INTRODUCTION	1
REVIEW OF LITERATURE	1
RESEARCH METHODOLOGY	4
VARIABLES.	6
ANALYSIS OF RESULTS.	7
DISCUSSION AND CONCLUSIONS	10
APPENDIX A	13
APPENDIX B	15
FOOTNOTES	18
SELECTED BIBLIOGRAPHY.	20

LIST OF TABLES

1. Test Results.	7
2. Relationship of Age and Breast Feeding-Test Group	8
3. Relationship of Age and Breast Feeding-Control Group.	8
4. Military Pay Grade of Study Participants.	9

INTRODUCTION

An increasing number of women in America are wanting to breastfeed their babies, but because of cultural prohibitions and lack of knowledge, many run into frustration in their attempts. Further, Sally Wendkos Olds, author of The Complete Book of Breastfeeding states:

The path to easy and natural breastfeeding is strewn with so much misinformation that many women have been unable to surmount the cultural taboos or the coercion of nurses and doctors who are against breastfeeding.¹

- The investigators felt that a short prenatal teaching session would
- help the mother who wishes to breastfeed achieve success.

REVIEW OF LITERATURE

The positive effects of breastfeeding have been recognized by the International Pediatric Association, who in a Seminar at Montreal in 1975 recommended an action program to encourage breastfeeding. The U.S. Commission on Nutrition also reaffirmed its position that breastfeeding should be encouraged.² However Brown states that there has been a lack of knowledge and experimental evidence concerning many questions relating to breastfeeding.³

"A Study of Infant Feeding Practices in Edinbourg" by T. R. Kirk reports incidences and durations of breastfeeding of ninety-four mothers having infants up to fourteen months old. At birth 42.5% of the mothers were breastfeeding. By two weeks of age this percentage had decreased to 29.8%. At one month only 27.2% and by four months only 10.2% were still breastfeeding. The author feels that although no health care professionals strongly encouraged bottlefeeding, many times they did not encourage breastfeeding.⁴

According to Countryman, often infants who are started on breast milk at birth leave the hospital either partially or totally weaned and many babies have been weaned by six to eight weeks of age. She feels that a major reason for this is inadequate antepartum breast care.⁵ La Leche League members described their hospital experience in one study as having been detrimental to successful breastfeeding.⁶

Nurses have been criticized for their lack of knowledge of breastfeeding and their lack of support for breastfeeding mothers. Evelyn M. McGreal, in her unpublished Master's Thesis described most nurses as not being helpful.⁷ Patricia J. Estok reports a study in which it was found that there is little correlation between nurses' perceptions and mothers' perceptions of problems in breastfeeding.⁸

Another study of La Leche League mothers and obstetrical nurses revealed conflicting perspectives of needs. Obstetrical nurses were concerned with new mothers getting their rest, disturbing other mothers, and leaving an infant with mucous problems for long periods of time with the inexperienced mother. The La Leche League mothers did not feel these were significant reasons for nurses to discourage breastfeeding.⁹ A study of 756 La Leche League members who attempted unsuccessfully to breastfeed, found that twenty percent stopped because of what they perceived as hospital or physician intervention. The author notes that "Lack of information is significantly related to all of the reasons why mothers stop breastfeeding before they wish."¹⁰

The importance of prenatal breastfeeding instruction has been alluded to but not well documented in the literature. Osorio, Diaz-Rossello, and Cappuro stress a strong need for the instructional component in breastfeeding success.¹¹ In the editorial "Breast is Best" from Developmental Medicine and Child Neurology, the need to integrate knowledge about breastfeeding with preparation for motherhood is recognized. The responsibility of education of adolescent and adult pregnant women is placed upon obstetricians, pediatricians, and nurses. The author goes on to state "We need to look carefully at our institutions such as mother care classes, antenatal clinics, labor wards, and lying in wards to make sure that breastfeeding mothers are welcome and get maximum support."¹²

Munally describes the useful approach of group classes in breastfeeding in her article "A New Approach to Helping Mothers Breastfeed."¹³

According to Dorothy Clapper Brack, the premise that societal forces have stifled knowledge about breastfeeding suggests the need for prenatal instruction and predicts an increase in the popularity of breastfeeding as a result of more widespread information.¹⁴

In view of previous evidence cited, the investigators agree with Ladas that "If we feel it is good for mothers to breastfeed we must develop programs to help them."¹⁵

RESEARCH METHODOLOGY

The Research Hypothesis is: Given that a primipara 32 weeks or more in pregnancy is planning to nurse the baby, an instructional unit will increase the probability that she will still be breastfeeding at one month after delivery.

Subjects were primiparas receiving care at clinics serving active duty and retired military and their dependants under the direction of the Commanding Officer, Walter Reed Army Medical Center.

The investigators first received permission from the Obstetrical Department, the Research Division, and the Department of Nursing to carry out the study. We then visited the two clinics involved and discussed the study with clinic personnel.

Third trimester primiparas in the clinic were asked how they planned to feed their babies. If they stated that they were interested in breastfeeding, the project was explained and permission forms were signed. (See Appendix A). A coin was then flipped and they were placed in either the research or control group.

Those in the control group were told we were evaluating the effectiveness of the current program at Walter Reed and a nurse on the post partum unit would assist them with any breastfeeding problems. They were also informed that we would contact them one month after delivery to see how they were feeding their babies.

Women in the research group were given a ten minute educational unit (see Appendix B) in addition to being told that a nurse on the post partum unit would be available to help them with any breastfeeding problems. They were also informed that we would contact them one month after delivery to see how they were feeding their babies.

All interviews were conducted on a one to one basis. At one clinic the researchers utilized the nurse's office. The other clinic was lacking for space so interviews were conducted in a corner of the waiting room.

Post delivery contact consisted of a telephone call to the subject. Format for the call was "How are you feeding your baby? If you are not breastfeeding would you mind telling us why you are not." Successful breastfeeding was defined for the study as continuing to breastfeed at least one feeding per day three to four weeks after delivery. The level of significance was set at 0.05.

VARIABLES

The independent variable was the educational unit. The dependent variable was success in breastfeeding.

Several confounding variables were identified. One important one was the previous knowledge of the breastfeeding population. We somewhat controlled this by utilizing only primiparas in our study. However at one clinic especially, we found that many of our subjects stated they were attending prepared childbirth courses which included a large segment on breastfeeding. The investigators felt we could not control the knowledge but could reduce its significance by random assignment to the research and control groups.

A second variable was that teaching would be done on a one to one basis by three nurses. In order to eliminate this variable close compliance with the teaching format was used and a practice session with all three nurses was conducted.

One of the research team was also a member of the nursing staff at Walter Reed Army Medical Center. As a part of her duties she was expected to help breastfeeding mothers on the post partum unit. Because of this she did not participate in the teaching segment of our study. She received a total listing of the participants in the study to determine the date of delivery. However she was not told how the groups were split or membership of the test or control groups.

Another variable was the "Hawthorne Effect". It is possible that because the women knew we were interested and would be calling after delivery, It might increase positive results. Also if we spent more time with the research group than the control group, just the time factor might influence results. To minimize this variable we tried to spend a significant amount of time with the members of the control group and emphasized the importance of their participation without giving them any information.

Analysis of Results

	Interviewed	Delivered	Breastfeeding	Not Breastfeeding	UTC [*]
Test Group	25	24	13	3	9
Control Group	25	25	10	4	11

Table 1 Test Results

A t-test was computed with no significant results. This will not allow the researchers to accept their hypothesis: Given that

* Unable to Contact (UTC) The reason for the loss of contact was largely due to midsummer military transfers

a primipara 32 weeks or more in pregnancy is planning to nurse the baby, an instructional unit will increase the probability that she will still be breastfeeding at one month after delivery.

A previous study done by Kirk in 1976 which indicated that only 57% of the mothers in the population studied who were breastfeeding at birth were still breastfeeding at one month after delivery.¹⁶ The study done at Walter Reed doesn't repeat the same findings. 80% of the test group mothers were breastfeeding after one month postpartum. 71% of the control group mothers were breastfeeding after one month postpartum.

The mean age of the primiparas interviewed in the study was 24.25 years and the range was from 16 to 31. Data relating to age and successful breastfeeding is shown in Tables 2 and 3.

Participant	Age	Breastfeeding	Not Breastfeeding	Undetermined
1	21	/		/
2	21			/
3	25	/		/
4	25	/		/
5	20	/		
6	30	/		
7	15		/	/
8	20			/
9	27	/		/
10	23	/		/
11	23	/		/
12	27	/		/
13	18	/		/
14	24	/		/
15	20	/		
16	20	/		
17	22		/	
18	19	/		
19	20			/
20	19	/		
21	23	/		/
22	19		/	/
23	20		/	
24	20	/		
25	23	/		

Table 2 Relationship of Age and Breastfeeding-Test Group

Participant	Age	Breastfeeding	Not Breastfeeding	Undetermined
1	28	/		
2	29			/
3	24			/
4	20	/		
5	30			/
6	20	/		
7	23			/
8	24	/		
9	28	/		
10	27	/		
11	26	/		
12	21			/
13	31			/
14	19			/
15	21	/		
16	23			/
17	20		/	
18	24			/
19	22		/	
20	25		/	
21	22		/	
22	20	/		
23	26			/
24	23			/
25	25	/		

Table 3 Relationship of Age and Breastfeeding-Control Group

In this sample the researchers found a wide range of ages of the women who were successfully breastfeeding. The mean age for postpartum mothers who were successfully breastfeeding in this sample was 22.6 with a standard deviation of 9.7 years. The range was eleven years from age twenty to thirty.

DISCUSSION AND CONCLUSIONS

The sample is too small for a detailed analysis. Not enough data was collected to reach any substantial conclusions. Our hypothesis: Given that a primipara 32 weeks or more in pregnancy is planning to nurse the baby, an instructional unit will increase the probability that she will still be breastfeeding at one month after delivery, could not be accepted on the basis of our data.

One weakness of this study in its present state is that no generalizations can be made beyond the army population that was sampled. Further restriction of generalization resulted from the large number of transfers out of the area.

Another weakness in drawing conclusions would be that not enough descriptive data was collected on the subjects. For example, it would have been advantageous to have known the number of bottle-feeders in the population of primiparas 32 weeks or more in pregnancy at the Walter Reed prenatal clinic. This data could have provided valuable information about the percentage of breastfeeding mothers as well as given a basis for comparison of age and socioeconomic status.

To further utilize questions mothers had concerning breastfeeding we would have profited by keeping a frequency tally in order to draw some conclusions about the teaching plan. One way in which improvements of data collection would be made is to formulate a questionnaire for descriptive data.

In addition to continuing the study of the relationship between prenatal teaching and successful breastfeeding, the investigators feel it would be appropriate to begin to look at other factors. One variable impressing the investigators was the apparent high motivation to breastfeed displayed by our subjects. This was especially indicated by two women who experienced complications in pursuing their plan.

A woman in the control group developed a fever in her first three postpartum days but expressed milk while her baby was bottlefed. Transition to total breastfeeding was successful after her elevated temperature subsided.

Another woman in the experimental group had to return to the hospital for one feeding each day until her baby was discharged ten days later. When the baby came home she increased to total breastfeeding.

Further evidence of strong motivation is obvious from women who were planning to return to work soon after their deliveries. This was demonstrated by their interest in eliciting the nurses' help in planning a breastfeeding schedule around their jobs.

The investigators suggest that the study should be repeated in other settings with larger groups of women. Other questions that we found during the study which need further research include: Do mothers who have cesarean sections have more difficulty breastfeeding? How can working mothers be helped to breastfeed successfully? Do multiparas need special help particularly if they were unsuccessful in previous attempts to breastfeed? If so what programs would be most helpful? When should breastfeeding programs begin, how long should they last and what should they include?

36 In a concurrent study being done on the postpartum ward at Walter Reed regarding number and types of telephone calls from new mothers, there appears to be a decrease in the number of telephone calls regarding breastfeeding problems. Further analysis should be made of this phenomenon and perhaps a correlation between the two studies should be planned regarding this factor!

Much needs to be learned about ways nurses can help mothers achieve satisfaction and success in breastfeeding their infants. It is the hope of the investigators that this study might encourage interest in further research.

Work Unit No.: 9035

Title of Project: Effects of Altitude, Mood and Dietary Habits on
Performance of a Choice-Reaction Time Task.

Principal Investigator: James P. Dixon, CAPT, USAF, RSC
C, Aerospace Physiological Rsch
Division of Aerospace Pathology
Armed Forces Institute of Pathology

Objectives: To evaluate the subtle influences of mood, altitude, dietary habits and other stresses on performance and to relate these decrements to the job performance of service personnel.

Technical Approach: By means of a choice-reaction time task, efficiency (number of correct divided by total time) will gauge performance. This will be related to the physiological parameters of arterial oxygen saturation, respiration and heart rates at various altitudes.

Progress & Results: When the first set of control runs (100% O₂) were compared to the experimental runs (compressed air at an altitude unknown to the subject), extreme decrements were found. In fact, a greater decrement in performance occurred with the mask and compressed air than occurred without a mask at the same altitude. This problem has not been resolved, but the appearance of hypoxia symptoms has implicated the mask. The test protocol now employs a nasal cannula instead of a mask and the experiment has been started over. Therefore, no results can be stated.

Funds: None requested at this time.

Interim Report: Please note that there has been some minor changes in the experiment. Specifically, they are as follows:

1. Nasal cannula replaces the mask.
2. Number of trials in the choice-reaction time task has been increased.

3. Flights may not include rapid decompressions to no more than FL450, with subjects closely monitored using an oximeter (O₂ saturation, heart rate, respiration rate measured) such that physiological parameters are not allowed above an equivalent 25,000 feet.
4. Principal Investigator is changed from Maj John Wolcott to Capt James Dixon.
5. Since altitude is presently the primary variable, other stresses will be studied in subsequent experiments after baseline values on performance have been established in these subjects.

WORK UNIT #9036

TITLE OF PROJECT: Urease and Deaminases in Chemistry and Medicine (NIH Grant).

SUBJECT: Clinical Investigation of Patients with Myo-Adenylate Deaminase Deficiency.

PRINCIPAL INVESTIGATOR: William N. Fishbein, M.D., Ph.D.

DATE OF APPROVAL AT WRAMC: 28 June 1977

COPY OF ANNUAL PROGRESS REPORT FY-77 IS ATTACHED:

Approval had been obtained for femoral vein aspiration in these patients, but we found antecubital vein blood satisfactory for disease diagnosis by measuring ammonia and lactate levels before and after exercise. Five patients have been tested thus far, three of them have been reported (see below). So far the test appears to be an effective screening tool, without significant side effects. No drugs have been used, and no funds from WRAMC.

PUBLICATIONS:

Fishbein, W. N., Griffin, J. L., and Armbrustmacher, V. W.: A New Disease of Muscle: Adenylate Deaminase (AMPDA) Deficiency. The Journal of Cell Biology 75: 321a, 1977.

Fishbein, W. N., Armbrustmacher, V. W., Griffin, J. L.: A New Muscle Disease: Myo-Adenylate Deaminase Deficiency; 144th National Meeting, AAAS, Washington, D.C., 2/12-17/1978. p. 148.

Fishbein, W. N., Armbrustmacher, V. W., Griffin, J. L.: Myo-Adenylate Deaminase Deficiency: A New Muscle Disease. Clinical Research, 26: 20A, 1978.

Fishbein, W. N., Armbrustmacher, V. W., Griffin, J. L.: Myoadenylate Deaminase Deficiency: A New Disease of Muscle. Science 200: 545-548, 1978.

TYPE OF REPORT: Interim

Work Unit No.: 9077

Title of Project: Peripheral Neuropathy and Chronic Obstructive Lung Disease - A Clinical and Electrophysiological Study

Investigators:

Principal: Alan Ira Faden, M.D., MAJ, MC

Associate: E. Mendoza, MAJ, MC
A.D. Huott, M.D., COL, MC

Objectives: To determine whether there exists clinical or subclinical peripheral nerve impairment in patients with chronic obstructive pulmonary disease (COPD) and if so, what duration and degree of pulmonary dysfunction is required to produce it.

Technical Approach: Patients are selected by the pulmonary section on the basis of a history compatible with COPD, and FEV of less than 50% of predicted, and the absence of conditions known to be associated with neuropathy. These patients are evaluated by standard neurological and electrophysiologic examination. The latter includes sensory and motor conduction velocities as well as sample EMG's when indicated.

Progress and Results: 16 patients have been studied to date; 12 had electrophysiologic evidence of a subclinical neuropathy. Of the abnormalities found, half involved only sensory nerves while half involved both sensory and motor nerves. Only two patients had clinical findings suggestive of neuropathy.

Conclusions: These findings indicate that subclinical sensory or sensorimotor neuropathy commonly occurs with COPD.

Funds Utilized: None

Funding Requirements: None

Publications: None

Type of Report: Interim

Work Unit No.: 9078

Title of Project: Encephalopathy Following Treatment of Chronic Pulmonary Failure: A Clinical and Electroencephalographic Study

Investigators:

Principal: Alan Ira Faden, M.D., MAJ, MC

Associate: R.W. Enquist, M.D., MAJ, MC

Objectives: To determine the frequency of the encephalopathy which may be seen following the treatment of chronic pulmonary failure and to distinguish the relative importance of the two presumed caused variables - alkalosis and aminophylline administration.

Technical Approach: Patients are to be selected by the ICU staff on the basis of clinical history, a PCO_2 of greater than 50, a pH of less than 7.25 and who are to be placed on respirators. Patients with evidence of other significant metabolic disturbances will be excluded. Clinical neurological and electroencephalographic examinations will be performed as soon as possible after admission and repeated in 6-12 hours. Routine arterial blood gases will be drawn as well as a serum aminophylline level at the time of the second EEG.

Progress and Results:) No patients have been found to date which meet
Conclusions:) the requirements described above.

Funding Utilized: None

Funding Requirements: None

Publications: None

Type of Report: Termination due to inability to find patients meeting the protocol requirements.

Work Unit No.: 9090

Title of Project: The Effects of Immunosuppressant on the Oral Environment.

Investigators:

Principal Investigator: Arthur Gross, COL DC

Coinvestigator: Everett K. Spees, Jr., COL MC

Objectives: To determine the alterations in oral bacteriology and immunological protective factors due to immunosuppressive agents following renal transplantation.

Work on the this protocol has been terminated due to lack of cooperation by patients and the subsequent departure of the coinvestigator, COL Everett K. Spees.

Work Unit No.: 9091

Title of Project: Candida Shifts and pH Changes in Patients with Oral Malignancies.

Investigators:

Principal Investigator: Arthur Gross, COL DC

Coinvestigators: John P. McCasland, COL DC
P.W. Murphy, MAJ DC
Elia Esposito, GS-12
D.F. Cutright, COL DC

Objectives:

a) To determine the relationship between the presence of Candida albicans in the oral cavity and the clinical appearance of mucosal inflammation, and to investigate the possibility of eliminating C. albicans, if present, by a method other than antifungal drug administration.

b) To determine post-treatment pH changes in saliva, on the surface of the teeth, and in selected areas of oral mucosa, and to correlate possible pH changes with the presence of C. albicans in the oral cavity.

Publication: IADR Abstracts 1978, Candida Shifts and pH Changes in Patients with Oral Malignancies. R.F. Godat, A. Gross, J.A. Setterstrom, C. Blanco, Dept of Dentistry and U.S. Army Institute of Dental Research, WRAMC, Washington, D.C.

Work on this protocol has been terminated due to difficulties encountered in the scheduling of patients and the departure of three of the coinvestigators, John P. McCasland, COL DC; P.W. Murphy, MAJ DC; and E.J. Esposito, DAC, GS-12.



DEPARTMENT OF THE ARMY
UNITED STATES ARMY INSTITUTE OF DENTAL RESEARCH
WASHINGTON, D.C. 20012

IN REPLY REFER TO:
~~XXXXXX~~
SGRD-UDZ


6 October 1978

SUBJECT: Annual Progress Reptot, Clinical Investigation Program, Work Unit #9094, Utilization of Biodegradable Copolymers of Polylactic and Polyglycolic Acid

COL Richard Evans
Clinical Investigation Service
Walter Reed Army Medical Center
Washington, DC 20012

1. The above reference and research project is still actively being considered at Federal Drug Administration but has not received final approval. Therefore as of this date there is no progress report.
2. As soon as approval/disapproval is received your committee will be immediately notified.

Sincerely,


DUANE E. CUTRIGHT
Colonel, DC
Commanding

DEPARTMENT OF THE ARMY
HEADQUARTERS WALTER REED ARMY MEDICAL CENTER
Washington, D.C. 20012

WRAMC Regulation
70-1

8 January 1979

Clinical Investigation Program

WRAMC RESEARCH ACTIVITIES

	Paragraph
Purpose	1
Criteria	2
Definitions	3
Committees	4
Clinical Investigation Committee	5
Human Use Committee	6
Chief, Clinical Investigation Service	7
Records and Reports	8
Reports to Pharmaceutical Companies	9
Request for Funds	10
Informed Consent	11
Research Involving Children.	12
Low Risk Protocols in Adults	13
Research in Pregnant Women Fetuses	14
Research, Mentally Infirm.	15

1. PURPOSE. This regulation prescribes the policies and procedures applicable to the Clinical Investigation Program within the patient care facility at Walter Reed Army Medical Center.

2. CRITERIA. Clinical investigation activities will meet the following criteria:

a. The objectives have scientific merit and are reasonably attainable.

b. The investigators are competent to perform the studies proposed.

c. Resources required for the proposed studies are either available, or can be obtained, and are proportionate to the merit of the proposal.

d. The studies will not have a deleterious effect upon the care of the sick and wounded.

*This Regulation supersedes WR 70-1, dated 1 April 1973

8 January 1979

e. The studies are performed in a considered, coordinated, and professional manner.

f. Whenever feasible, studies should be initially performed in animal models.

g. The rights, well-being, and dignity of human subjects are maintained in accordance with the principles of the Declaration of Helsinki of the World Medical Association, and that written consent is obtained when indicated.

h. Any research involving animals will conform with AR 70-18 and the Laboratory Animal Welfare Act (Public Law 89-544; 7 USC 2131 et seq).

i. Assure compliance with existent military regulations to include AR 40-7, Use of Investigational Drugs in Humans; AR 40-37, Radioisotope License Program (Human Use); AR 70-25, Use of Volunteers as Subjects of Research; and WRAMC Reg 40-10, Health Physics Regulation; AR 40-38, Medical Services Clinical Investigation Program.

j. The voluntary consent of each adult human subject is essential. Each individual who initiates or directs the clinical investigation has a personal duty and responsibility for ascertaining the quality of the subject's consent. Before the acceptance of the subject, he must be given adequate explanation. He must be informed of the nature, duration and purpose of the study; the methods and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the study. He should be informed of any benefits he may acquire from participation in the study, and if there should be no benefits, the participant should be so informed. The process of obtaining voluntary consent must be witnessed by an observer who is not a coinvestigator on the research protocol. Written consent will be obtained in accordance with the format outlined in the appendix and will be in nonmedical language that is easily understood by the subject. The investigator will be required to maintain copies of the written voluntary consent for five years following completion of the study. Copies of the consent forms for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number.

k) Children older than age seven, unless incapacitated, must assent (See definition section for definition of assent.) to participation in studies. Additionally, the written consent of the parent or

8 January 1979

WR 70-1

guardian must be secured and properly witnessed. An effort should be made to secure the written consent of the child utilizing a consent form written at his age level. In addition, "instructions to guardian" may need to be prepared that is written at an adult level. Both the processes of assent and securing written consent should be directed toward providing the patient and parent (guardian) the information given to adult volunteers, i.e., the nature, duration and purpose of the study, the methods and means by which it is to be conducted, etc.

3. DEFINITIONS.

a. Clinical investigation under this program consists of the organized scientific inquiry, both in humans and by directly related laboratory work, into clinical problems of significant concern in the necessary health care of members of the military community, including active duty personnel, dependents, and retirees. Clinical investigation at WRAMC shall include projects involving WRAMC patients, investigators, or facilities.

b. Subjects are any persons who may be at risk because of participation as an object of clinical investigation by members of the AMEDD or their appointed representatives. These may include inpatients, outpatients, organ donors, informants, or normal individuals who participate in studies of medical, physiological, sociological, or psychological orientation. Selection of subjects must be equitable.

c. At risk: A person is "at risk" if he/she may be exposed to the possibility of harm (physical, psychological, or sociological) as a consequence of activity which extends beyond use of established and accepted methods necessary to meet his/her needs. Determination of nature and extent of "at risk" is a matter of common sense and professional judgment. In most cases, utilization of someone's time (inconvenience) will constitute "risk" since the activity is not an accepted method to meet the person's needs. Responsibility for this determination resides at all levels of institutional and departmental review.

d. Children: Persons who have not attained the legal age of consent to general medical care as determined under the law of the jurisdiction in which the research is to be conducted (DC - age 18).

e. Research: A formal investigation designed to develop or contribute to generalizable knowledge. This may involve dietary manipulations, alteration of daily routine or environment, questionnaires, record review.

8 January 1979

f. Minimal Risk in Children: The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of healthy children. Examples include immunization, modest changes in diet or schedule, obtaining blood and urine specimens, and most behavioral research.

g. Assent: A child's affirmative agreement to participate in research which can only be given following an explanation appropriate to the level of understanding of the child. It is recognized that "assent" may have no legal status and may be difficult to obtain in young children; nevertheless, some sort of opportunity should be offered the child to agree to participate. (Ref Federal Register 43:2084-2114, Jan 13, 1978, and 43:31786-31794, Jul 21, 1978.)

4. COMMITTEES: The following committees will be appointed. At the option of the Chairman, the Clinical Investigation Committee and the Human Use Committee will meet either separately or simultaneously.

a. Clinical Investigation Committee: To review all clinical investigation proposals for scientific adequacy and to establish priorities for support. For the purpose of recommending new drugs which have not been released by the Food and Drug Administration, the Committee will serve also as the Therapeutic Agents Board (para 126, AR 40-2). This committee will be composed of a representative from each of the following:

Director, Medical Education (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Medicine
Rotating Service Chief from Department of Medicine
Chief, Department of Surgery
Rotating Service Chief from Department of Surgery
Chief, Department of Pathology
Chief, Department of Radiology
Chief, Department of Pediatrics
Chief, Department of Psychiatry
Chief, Department of Obstetrics and Gynecology
Commander, USA Dental Activities (DENTAC)
Director, WRAIR
Chief, Nuclear Medicine Service
Chief, Health Physics
Chief, Pharmacy Service
Director, Patient Administration Directorate
Chief, Nursing Research Service
Assistant Chief, Clinical Investigation Service
A rotating senior clinical investigator (list to be established
by Chief, Clinical Investigation Service)
Representative (USUHS)

8 January 1979

WR 70-1

The attendance of each member will be recorded in the minutes.

b. Human Use Committee: To review for medical safety and suitability all clinical investigation protocols involving the use of human subjects. This committee will be composed of a representative from each of the following:

- Director, Medical Education (Chairman)
- Chief, Clinical Investigation Service (Secretary)
- Chief, Department of Clinical Pastoral Service
- A Legal Counsel
- Chief, Department of Nursing
- Chief, Department of Psychiatry
- Chief, Department of Obstetrics and Gynecology
- Chief, Nuclear Medicine Service
- Command Sergeant Major
- Director, Human Resources Directorate
- CDR, USA Dental Activities (DENTAC)
- Clinical Pharmacist, Hematology-Oncology Service
- Assistant Chief, Clinical Investigation Service
- Patients' rights representative
- Representative (USUHS)
- Director, Patient Administration Directorate
- A rotating senior clinical investigator (list to be established by Chief, Clinical Investigation Service)

The Attendance of each member will be recorded in the minutes.

c. Radioactive Drug Research Committee (RDRC): To review all research protocols using radioactive drugs in human subjects, and to insure that such protocols are in compliance with the Code of Federal Regulations, Title 21, Chp 1, Part 361. All protocols utilizing radioactive drugs will include radiologic assessment data, as an appendix to the protocol, including name of the radionuclide, presence of any contaminants, maximum dose to be administered, radiation absorbed doses to whole body and other organs accumulating the isotope, dosage from any X-ray procedures that are part of the research study, and any limitation regarding patient population due to sex and age. A report will be made by the RDRC to the Clinical Investigation Committee regarding each radioactive drug protocol in humans. In addition, the Committee will be responsible for preparing the annual report on research use of a radioactive drug to the FDA. This Committee will be composed of at least five individuals, including Chief, Nuclear Medicine Service; Chief, Health Physics; Chief, Clinical Investigation Service; Nuclear Medicine Service Pharmacist; and Chief, Radiation Therapy Service.

8 January 1979

The RDRC will select a chairman, who will sign all applications, minutes, and reports of the Committee as well as a secretary. The RDRC will meet at least quarterly. A quorum consisting of a majority of the membership must be present, with attendance of at least individuals who are specialists in nuclear medicine, radioactive drug formulation, and radiation safety and dosimetry. Minutes will be kept, including numerical results on voting. No member shall vote on a protocol in which he is an investigator. The RDRC will submit an annual report to the FDA prior to 31 January of each year.

The investigator must submit a report (Appendix C) and a copy of the signed consent form to the RDRC within 15 days from the date of administration of the isotope.

d. Functions of the Committees: Either the Clinical Investigation Committee or Human Use Committee can terminate any investigation or place restrictions on a study at any time the Committees become concerned about the scientific merit of the study or adequacy of protection of human subjects. The Chief, Clinical Investigation Service can order a cessation of activity in any study pending an evaluation of the circumstances.

5. CLINICAL INVESTIGATION COMMITTEE: The Clinical Investigation Committee will meet once monthly, usually on the fourth Tuesday at 1400 hours. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals, either involving WRAMC patients, investigators, or facilities. Their review of proposals will address in particular scientific design, merit and funding. Departmental chairman will not vote on protocols from their own department, nor will any member vote on any protocol in which he is a coinvestigator. Periodically, the Committee will review approved and ongoing research. Each project will be reviewed at least once yearly, at the termination of the research and whenever there is a change either in the goals or the procedures or drugs used in human subjects, or deviation from the approved protocol. Adverse reactions to investigational drugs or procedures will be promptly reported to the Committee. The Committee will make recommendations to the Commander. Two-thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. There will be no proxy voting. Investigators will be informed within one week of the meeting in writing of the approval/disapproval of the project and reasons for so doing. A disapproved protocol must be resubmitted for approval. The Committee

may elect to approve a study with the addition of certain minor restraints/modifications. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAMC but cannot overrule the disapproval of the Committee. Appendix D outlines the administrative methods by which primary and secondary review of protocols and review of annual progress reports will be achieved.

6. HUMAN USE COMMITTEE: The Human Use Committee will meet once monthly, usually on the fourth Tuesday either concurrently or with the Clinical Investigation Committee following the Clinical Investigation Committee meeting. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals in which human subjects are used. Their review of proposals will address in particular, the protection of human research subjects. Periodically, at least once yearly, the Committee will review approved and ongoing investigational studies in which humans are used. Each project will be reviewed at least once yearly and whenever there is a change in the goals or the procedures or drugs used in human subjects. The Committee will make recommendations to the Commander. Two thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAMC but cannot overrule the disapproval of the Committee. There will be no proxy voting.

7. CHIEF, CLINICAL INVESTIGATION SERVICE.

a. Shall function as secretary/recorder at meetings. He will summarize the discussion on issues. Records of institutional review board's activities will be retained indefinitely.

b. Can terminate any project at any time pending Clinical Investigation Committee and Human Use Committee review.

c. Will be the contact with the Commander to assess availability of resources to support projects and will manage those resources with guidance from Committees and Commander.

d. Will keep the Commander and Committees informed of the continuing changes in FDA/NIH requirements.

e. Will supervise under the guidance of the Clinical Investigation Committee and Human Use Committee, the secretarial/administrative support staff to support clinical research and insure compliance with regulations.

8 January 1979

f. Will advise the Clinical Investigation Committee regarding alternatives if priorities for support need to be established.

8. RECORDS AND REPORTS.

a. Initial Protocol. Requests for initiating research projects will be submitted in one copy to the Commander, Walter Reed Army Medical Center, ATTN: Chief, Clinical Investigation Service. This will be submitted by the principal investigator through the chief of the respective service and department, and prepared as described in Appendix A. Protocols which do not conform to Appendix A will not be accepted by the Chief, Clinical Investigation Service. Frequent deficiencies in protocols include omission of an impact statement, failure to state the time required to complete the project, failure to include budget information, and failure to include signatures of the respective chief of service and department. When radiological, laboratory, or nursing support is required, the principal investigator should have obtained the concurrence of the appropriate chief of service prior to submission to the Clinical Investigation Committee. The chief of the department proposing the study will provide an indorsement that the proposal conforms to the criteria described in paragraph 2 above. To be placed on the agenda for the monthly committee meeting, the research protocol must be received by the 25th of the month preceding the meeting. Protocols will be distributed to the Committee members at least one week prior to the meeting, with appropriate agenda. Under no circumstances will a project require greater than three years to complete. If more than three years are needed, submission of a new protocol will be required.

b. Addenda to Initial Protocols. Whenever there is a change either in the goals or the procedures or drugs used in human subjects, the investigator will submit an addendum to the Commander thru the chief of the respective service and department, and Chief, Clinical Investigation Service. If necessary, the Committee will review this addendum as a new research proposal.

c. Annual Progress Reports: Annual progress reports will be prepared for each approved project as prescribed by AR 40-38, Clinical Investigation Program and will be submitted to Clinical Investigation Service prior to 15 August of each year until the investigation is completed. See Appendix B. Accurate preparation of budgetary data and/or documentation of abstracts or publications is essential. Failure to submit an annual progress report will result in termination of the project and withdrawal of the principal investigator's privilege to function as a principal investigator in any project.

d. Interim Reports. Interim reports must be submitted at any time when important development, adversities or other circumstances occur which should be brought to the attention of higher headquarters. In particular, interim reports must be submitted when unexpected deaths or harmful side effects occur during the course of an investigation. Interim reports are required within three working days of the

development. They will be considered by the Chief, Clinical Investigation Service, who may elect to suspend work on the investigation until the Committee has an opportunity to meet.

e. Final Reports. Final reports are required upon completion or termination of a specific research effort. The report will include a summary of all work performed, results obtained, together with copies of all publications, whether printed, in press or submitted for publication. Inclusion of references to previous progress reports is optional. If the project is terminated prior to completion, the reasons for termination should be reported. Report is due within 30 days following completion or termination of effort.

f. Special Therapeutic or Diagnostic Procedures. Any special therapeutic or diagnostic procedures or any new, hazardous, or otherwise noteworthy therapeutic or diagnostic measures will be recorded in Space 24 of DA Form 8-274, Clinical Record Cover Sheet for Inpatients.

g. All reports will be forwarded to the Clinical Investigation Service following review by the appropriate chief of service and department. The Clinical Investigation Service will schedule presentations to the appropriate hospital review committees. Following review by the Commander of committee reports the Clinical Investigation Service will insure that reports are forwarded to the Surgeon General as required by AR 40-38.

h. Radioactive Drug Protocols Involving Administration of Radioactive Drugs to Humans. The investigator must submit a report (Appendix C) and a copy of the signed consent form to the Radioactive Drug Research Committee (RDRC) within 15 days from administration of the isotope.

i. Volunteer Agreements. Copies of volunteer agreements for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number (see Appendix A).

8. REPORTS TO PHARMACEUTICAL COMPANIES. For procurement of investigational drugs which have not yet been released by the Food and Drug Administration, detailed reports to the drug company are required by FDA (Form FD 1573). The reports are the responsibility of the principal investigator, and are a matter of direct communication between him/her and the drug company.

9. REQUEST FOR FUNDS. Requests for funds to support the clinical investigation program are presented to the Center Command annually during the month of March.

a. Projects requiring refunding in the amount of \$1,000 or more are submitted each year prior to 1 March in the format of Appendix A for consideration. Projects requiring substantial increases (> 20% increase) in funding must undergo review by the Committee before funding will be approved.

b. New proposals which require funds may be submitted at any time. Approval of funding is dependent upon availability of local, Health Services Command or Surgeon General resources. Format Appendix A.

10. INFORMED CONSENT.

a. Patient Consent. The utilization of drugs or procedures which have not yet been accepted or established by common use require the patient's consent. The patient must be informed, i.e., his/her consent must be based upon his/her having knowledge of the experimental nature, purpose, and possible hazards. The consent should be in writing, except as provided in paragraph 7b, AR 40-7, or if the patient is a child (see 11). The consent form must be witnessed by someone other than an investigator on the project. Copies of the written voluntary consent will be maintained by the principal investigator for five years after termination of the study and will be forwarded to the Chief, Clinical Investigation Service, within 30 days of entry of the patient onto study.

b. Human Volunteer. Investigative studies in which drugs are employed are subject to, and must comply with AR 40-7, Use of Investigational Drugs and/or AR 70-25, Use of Volunteers as Subjects of Research in addition to AR 40-38.

11. RESEARCH INVOLVING CHILDREN.

a. In general, research in children will not be undertaken unless appropriate studies have first been undertaken in animals, adults, or older children. If the project is minimal risk, it may be undertaken if the Clinical Investigation Committee and Human Use Committee have approved the protocol, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured.

8 January 1979

WR 70-1

b. If the project is more than minimal risk, research that has potential direct benefit to the child, may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, considering that the risk is justified by the anticipated benefit, that the risk benefit ratio is at least as favorable as that presented by alternative approaches, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured.

c. If the project is more than minimal risk and of no direct benefit for subjects, the research may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, that the procedure presents experiences commensurate with those inherent in their actual medical situation and is likely to yield generalizable knowledge about the subject's condition, the knowledge is of vital importance, the assent of the child capable of understanding (possibly in writing) is obtained, and written permission of the parent or guardian is secured.

d. Appendix A includes the appropriate volunteer agreement for protocols involving research in children. On the opposite side must be "instructions to guardian" and if the project is directed at children capable of understanding written instructions, there must be "instructions to patient" written at a level comprehensible by the average aged participant in the project.

e. The Human Use Committee will periodically monitor the process of assent and permission in research involving children.

12. LOW RISK PROTOCOLS IN ADULTS. A protocol in which there is a minimum possibility of injury to the subject's health or rights as a result of the study. The study may not involve an investigational drug or device and may involve only human subjects who have given fully informed consent. That is, the study may not involve subjects who are minors, prisoners, institutionalized mentally infirmed or mentally disabled. The study also may not include subjects temporarily mentally disturbed by reasons of unconsciousness or coma. Low risk protocols may be undertaken after local approval by the Clinical Investigation Committee and Human Use Committee. These protocols will continue to be forwarded to the Human Use Review Office, who will notify the Chief, Clinical Investigation Service, immediately if there is any difficulty with either the protocol or the assessment of level of risk. The following types of procedures are examples of low risk studies:

a) Collection and analysis of additional small amounts of cerebrospinal fluid, amniotic fluid and venous or arterial blood when taken in conjunction with specimens of these fluids which are to be drawn for accepted clinical indications and do not require another puncture to obtain the additional amounts of these fluids for investigational purposes.

b) Analysis of hair and nail clippings collected in a nondisfiguring manner and the analysis of deciduous teeth.

c) Collection for analysis of excreta and external secretions including feces, urine, sweat, saliva, cerumen and tears or swab culture specimens of body orifices, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during delivery.

d) Recording of data by physical sensors applied either superficially or at a distance and which do not involve significant input of energy into the subject. Such procedures include, but are not necessarily limited to weighing, electrocardiography, electromyography and detection of naturally occurring radioactivity, electroencephalogram, thermography, diagnostic echography and electroretinography, caliper measure of anthropomorphic characteristics and detection of naturally occurring radioactivity.

e) Blood drawing of quantities of blood less than 20 cc/6 weeks from adult subjects in whom their underlying medical condition is not known to be associated with anemia. These patients need not have a hematocrit done before obtaining the blood specimens.

f) Blood drawing of quantities of blood less than 450 cc/6 weeks or 12% of the estimated blood volume, 7% of the body weight, whichever is lesser, from subjects who are not anemic. (Anemia is defined as a hematocrit ≤ 40 for males, ≤ 35 for female and a reticulocyte count $> 1.5\%$). If quantities of blood > 20 cc/6 weeks are to be obtained, the protocol must state that a hematocrit and reticulocyte count be obtained in patients prior to entry onto study and be not anemic.

g) Studies involving generally accepted, medically indicated diagnostic or therapeutic procedures or comparisons of two or more generally accepted alternative procedures.

h) Nonroutine or additional analysis of anatomical or biopsy specimens removed as the sole consequence of a widely accepted surgical indication.

i) Collection of both supra- and subgingival plaque, provided the procedure is no more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

j) Voice recordings made for research purposes such as investigations or speech deficits.

k) Moderate exercise by healthy volunteers.

l) The use of survey research instruments (interviews or questionnaires) and psychological tests, interviews and procedures that are part of the standard battery of assessments used by psychologists in diagnostic studies and in the evaluation of judgmental, perceptual, learning and psychomotor processes, provided that the subjects are normal volunteers and that the data will be gathered anonymously or that confidentiality will be protected by procedures appropriate to the sensitivity of the data.

m) Program evaluation projects that make no extra requirements on the subjects participating in the program and that will not benefit the subjects in the program.

n) Noninvasive pulmonary function testing such as (but not limited to) spirometry and plethysmography.

o) Collection and analysis of small amounts of internal secretions such as gastric contents and pulmonary aspirates when collection of these secretions does not involve the placement of either a nasogastric tube or endotracheal suction tube solely for obtaining specimens for research purposes.

p) Diary recordings of dietary intake, symptoms, physical activities and the like, whether the diarist remains anonymous or not.

13. Research in Pregnant Women Fetuses -- shall conform to the requirements of CFR 46.205 - 46.208.

A. General limitations.

1. No activity to which this subpart is applicable may be undertaken unless:

a) Appropriate studies on animals and nonpregnant individuals have been completed;

b) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

8 January 1979

c) Individuals engaged in the activity will have no part in:
(i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

d) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

2. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

B. Activities directed toward pregnant women as subjects.

a) No pregnant women may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:

1) The purpose of the activity is to meet the health needs of the mother;

2) His identity or whereabouts cannot reasonably be ascertained;

3) He is not reasonably available;

4) The pregnancy resulted from rape.

C. Activities directed toward fetuses in utero as subjects.

1. No fetus in utero may be involved as a subject in any activity covered by this subpart unless:

a) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

b) The risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

2. An activity permitted under paragraph (1) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, that the father's consent need not be secured if:

a) His identity or whereabouts cannot reasonably be ascertained,

b) He is not reasonably available, or

c) The pregnancy resulted from rape.

D. Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

1. Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

a) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

b) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(c) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

8 January 1979

WR 70-1

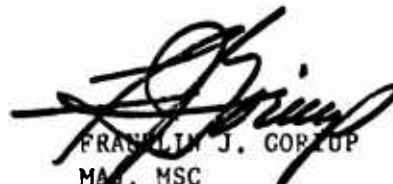
a) In the event the fetus ex utero is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

b) An activity permitted under paragraph (1) or (2) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

14. RESEARCH, MENTALLY INFIRMED. An appropriate addendum to these regulations will be published when the federal regulations regarding research in the mentally infirmed are promulgated.

HSWP-QCR

FOR THE COMMANDER:


FRANKLIN J. CORLUP
MAJ, MSC
ADJUTANT

DISTRIBUTION:

I plus 100 copies to
Clinical Investigation Svc

8 January 1979

WR 70-1

APPENDIX A

APPLICATION FOR CLINICAL INVESTIGATION PROJECT
(New protocols must conform to this format and be complete.)

1. PRINCIPAL INVESTIGATOR:
2. PROJECT TITLE: (Enter short project title.)
3. OBJECTIVE: (Brief but specific statement of the objective of the project.)
4. MEDICAL APPLICATION: (Explain briefly the medical importance and possible usefulness of the project.)
5. STATUS: (What has been accomplished or published in the proposed area of study and in what manner will the project relate to or differ from that which has been accomplished. If references or personal communication with other Army medical facilities are involved, so indicate.)
6. PLAN: (Outline exactly what is proposed to be accomplished in sufficient detail to indicate a clear course of action. Technological validity of procedures and chronological steps should be shown.)
(NOTE: The Surgeon General and the local Commander must have a very clear picture of how the investigation will proceed to meet the objective of the project. This paragraph frequently furnishes the basis for approval or disapproval of the project.)
7. BIBLIOGRAPHY: (List source of information.) (Include pertinent references and attach.)
8. FACILITIES TO BE USED: (Such as laboratory, ward or clinic.)
9. TIME REQUIRED TO COMPLETE: (Give month and year of expected start and anticipated completion. Under no circumstances will projects be funded for longer than three years without submission of a new protocol).
10. PERSONNEL TO CONDUCT PROJECT: (List names and positions of persons to be directly involved in project work. Attach short biographical sketch, including resume of education, research training, and list of publications, for each person named.)

8 January 1979

11. FUNDING IMPLICATIONS: (List total budget for the protocol, as well as the budget for the FY in which the protocol is approved.)

	<u>FY-78</u>	<u>Total for the Protocol</u>
a. Personnel: (itemize and explain need)	\$ _____	\$ _____
b. Equipment: (itemize and explain need)	_____	_____
c. Consumable Supplies: (itemize)	_____	_____
d. Travel: (itemize and explain need)	_____	_____
e. Modification of Facilities: (explain)	_____	_____
f. Other (explain)	_____	_____
TOTAL	_____	_____

12. DATE PREPARED: (give day, month and year of preparation)

(Signature of Principal Investigator)

(Signature of Department Chief)

(Enter title and mailing address of Principal Investigator)

8 January 1979

WR 70-1

APPENDIX A

IMPACT STATEMENT

(Must be attached to each protocol enumerating impact considered to be beyond good patient care.)

Patients:

Bed Occupancy:

Laboratory:

Radiology:

Pharmacy:

Nursing Service:

Registrar:

Other:

Approvals

Chief of Service

Chief of Dept

For Hosp Comm

Date:

Signature:

Name:

Grade:

Position:

8 January 1979

WR 70-1

APPENDIX A

VOLUNTEER AGREEMENT

Work Unit # _____

I, _____, having attained my eighteenth (18th) birthday, and otherwise having full capacity to consent, do hereby volunteer to participate in an investigational study entitled:

_____ under the direction of _____
_____ of the Department/Service/Institute of _____,
Walter Reed Army Medical Center,
Washington, D.C.

The implications of my voluntary participation; the nature, duration and purpose of the study; the methods and means by which the study is to be conducted; and the known inconveniences and hazards have been thoroughly explained to me by the principal investigator or by one of the coinvestigators and such inconveniences and hazards are set forth in detail on the attached page of this Agreement, along with my initials or signature. I have been given an opportunity to ask questions concerning this investigational study and my participation in the study, and any such questions have been answered to my full and complete satisfaction.

During the course of my treatment as a patient at Walter Reed Army Medical Center, I have been provided with a copy of a Privacy Act statement (DD Form 2005) which has made me aware of the safeguards available to me because of the Privacy Act of 1974. I have been given the opportunity to review the DD Form 2005, ask questions and to retain a personal copy. I have been made aware that the information gained about me, because of my participation in this investigational study, may be publicized in medical literature, discussed as an educational model, and used generally in the furtherance of medical science. I freely consent to provide such personal information as is requested of me for this investigational study and freely consent to the disclosure of pertinent personal information derived from my participation in this investigational study for reasons of publication in medical literature, discussion as an educational model and for those additional reasons which specifically relate to the furtherance of medical science.

I understand that in the event of physical injury resulting from the research procedures, medical treatment for injuries or illness is available and that compensation may be available through judicial avenues.

8 January 1979

I am aware that at any time during the course of this investigational study I may revoke my consent and withdraw from this study, without prejudice; however, I may be requested for medical reasons to undergo further examinations if in the opinion of my attending physician such examinations are necessary for my health or well being.

If there is any portion of this explanation that you don't understand, ask your doctor before signing.

Signature

Date

Printed Name

Social Security Number

Address (permanent)

I was present during the explanation referred to above, as well as during the Volunteer's opportunity to ask questions. I hereby witness the Volunteer's signature.

Signature

Date

On this page of the Volunteer Agreement, the principal investigator should set forth full details concerning the investigational study, insofar as such would affect or influence the tentative subject in any way. This explanation should be worded so that it can be clearly understood by the subject. The subject should place his initials at the end of the last line of explanation.

A proper explanation should, at a minimum, provide the answers to the following questions in lay language:

1. What will be administered or done to the subject?
2. How long will the subject's participation last?
3. To what tests or examinations will the subjects be required to submit?
4. Why is the investigation being conducted?
5. Has this particular study been done previously, and, if so, with what results?
6. What inconveniences or discomforts is the subject likely to experience?
7. What risks or hazards can be reasonably anticipated?
8. What steps will be taken to prevent or minimize these risks or hazards?
9. If blood is being drawn in the study, the total amount of blood should be accurately quantitated in both cc's and ounces.
10. The volunteer should be offered the opportunity to ask questions.
11. Alternatives to participation in the study should be identified. It Should be emphasized that participation in the study is entirely optional.
12. An instruction that the subject is free to decline participation or terminate participation at any time without prejudice.
13. Can the patient expect to accrue any benefit from participation in the study; if none, so state.
14. A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study.
15. Exculpatory language should not be used.
16. For Oncology protocols, where applicable, a statement that "there is no guarantee that the proposed chemotherapy program is better than a standard program".

8 January 1979

WR 70-1

APPENDIX A

VOLUNTEER AGREEMENT

(Children Under Legal Age of Consent or Adults Not Competent
to Give Informed Consent)

I/We _____ having fully capacity to
consent for my/our _____, _____, to
Relationship Name of Participant
participate in an investigational study entitled: _____

_____, under the direction of _____.
The implications of his/her participation; the nature, duration and
purpose; the methods and means by which it is to be conducted; and the
inconveniences and hazards which may reasonably be expected have been
explained to me/us by _____, and are
set forth on the reverse side of this Agreement, which I/we have
initialed. I/we have been given an opportunity to ask questions
concerning this investigational study, and any such questions have
been answered to my/our full and complete satisfaction.

I/we understand that I/we may at any time during the course of the
investigational study revoke my/our consent, and withdraw the above
named participant from the study without prejudice; however, he/she
may be requested to undergo certain further examinations, if in the
opinion of the attending physician, such examinations are necessary
for his/her health or well being.

I understand that in the event of physical injury resulting from the
research procedures, medical treatment for injuries or illness is
available and that compensation may be available through judicial
avenues.

An effort has been made to explain the research study to the child in
his language and my child agrees to participate.

Signature

Relationship

Date

Printed name

Social Security #, if available

Permanent address

Signature

Relationship

Date

I was present during the explanation referred to above, as well as the
parent's/guardian's opportunity for questions, and hereby witness
their signature.

Witness Signature

Date

APPENDIX B

Annual Progress Report FY

Work Unit No.:

Title of Project:

Investigators:

Principal: (senior investigator responsible for project)

Associate: (coinvestigators)

Objectives: (goal of research)

Technical Approach: (method of attaining objectives)

Progress and Results: (organized description of the research effort in relation to this work unit which was performed during the period of this report. If investigational drugs were used the information required by AR 40-7 must be included. The number of patients studied must be precisely delineated.)

Conclusions: (concise statement of goals achieved by current studies)
Have there been serious or unexpected side effects/ complications occurring in subjects participating?

Funding Requirements: (present and next FY)

Personnel: (name and grade)

Equipment:

Supplies:

Travel:

Other:

Publications: (list only those published during present FY or abstracts from your service which are related to the research described in this report. Failure to enumerate publications or abstracts may compromise funding of the protocol.)

Type of Report: (completed, terminated, interim)

(Report should be typed on 8 x 10-1/2" bond paper with 1" margins on all four sides. Do not number pages. Double space between sections of the report. Single space typing within each section. Do not put a signature block on report.)

DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-QCR

Radioactive Drug Research Report

TO Secretary, RDRC
Room 3E05, CIS
WRAMC

FROM

DATE

CMT 1

1. Work Unit #: _____
2. Work Unit Title: _____

3. Patient Information:
 - a. Identification Code: _____ (This number must allow for referencing back to a specific patient)
 - b. Age: _____
 - c. Sex: _____
 - d. Weight: _____
4. Pharmacological Dose Information:
 - a. Active Ingredients: _____
 - b. Maximum Amount Administered per Subject: _____
5. Radionuclide Information:
 - a. Radionuclide Used (Include any significant contaminants): _____
 - b. Activity of Radionuclide Used: _____
 - c. Date Radionuclide Administered: _____
6. Were X-ray procedures utilized in conjunction with this research protocol? YES _____ NO _____
7. Has any subject used in this study participated in other radioactive drug research studies? YES _____ NO _____

SIGNATURE OF RESPONSIBLE INVESTIGATOR

34

Encl #1

	YES	NO
9) A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study.		
10) For Oncology protocols, a statement that "there is no guarantee that the proposed chemotherapy program is better than a standard program"		
B. Is the language used in the consent form comprehensible by lay patients?		
C. Is there exculpatory language in the protocol?		

Signature _____

Date _____

Form for Primary and Secondary Review of Protocols

Protocol Title: _____

Reviewer: _____

Recommendations to the Committee:

☐ approval ☐ disapproval ☐ provisional approval
with stipulation

Narrative justification for recommendations:

Prioritization (Assign a number between 1 and 5, with 1.0 being outstanding, 3.0 average, and 5.0 disapproval.)

Scientific merit _____ (Assign a number)

Priority for funding _____

Is the budget realistic and adequately justified?

Incl #2

Dear Professional Committee Member of Clinical Investigation
Committee:

Enclosed is the FY-1978 Annual Progress Report (APR) for Work Unit #

It is requested that you represent the Clinical Investigation Committee by reviewing the APR for the enclosed protocol. Upon request, we will provide you with the original protocol, or you may come to the Clinical Investigation Service office during duty hours. The following questions are offered to you as guidelines to assist you in your review.

- 1) Is progress being made on the protocol?
- 2) Does the progress report indicate substantial deviation from the original protocol?
- 3) Is there any evidence of either unexpected side effects or an increased incidence of expected untoward side effects?
- 4) Is the request for funding appropriate? (One should consider here the merit of the project, previous budget, previous progress as documented by abstracts or publications, and justification for funding in the APR.)

Comments:

Recommendations: (please check in box)

- ☒ 1) That the APR and request for funding be approved by the Committee.
- ☒ 2) That the following additional information/clarification be furnished by the principal investigator.
- ☒ 3) That the entire Committee closely scrutinize this APR and examine the following specific aspects of the APR.

Signature

Date

encl #3

APPENDIX D

I. Implementation of the System of Protocol Review (including the System of Primary and Secondary Reviewers).

A. Protocols must be received by the 25th of the preceding month (or next working day if the 25th is a weekend day or holiday) in order to be considered at the next meeting, usually the fourth Tuesday of each month. Protocols not approved by the Department and Service Chief would not be accepted. The investigator would be expected to provide Clinical Investigation Service with several key references from the bibliography of the protocol.

B. Upon receipt of the protocol by Clinical Investigation Service, an administrative review and evaluation of the consent form would be undertaken. (See Incl #1 explanation and review sheet.) Any protocol with deficiencies would not proceed further in the review process until the deficiencies were resolved. Minor deficiencies in the consent form would be corrected by the editorial staff in the Clinical Investigation Service office. The investigator would receive a revised consent form and an explanation for revisions.

C. Protocols would then be read and reviewed by Chief and Asst Chief, Clinical Investigation Service, who would evaluate them primarily for adequacy of experimental design. The Chief and Asst Chief might elect to have an outside consultant review some protocols.

D. These protocols judged to be of reasonably sound design would be forwarded on about the first of the month to two (2) primary reviewers and two (2) secondary reviewers. The primary and secondary reviewers would be members of the Committee. Any of the primary and secondary reviewers could utilize additional consultation. An attempt would be made to select primary reviewers from the Committee on the basis of knowledge/expertise allied with the area under investigation in the project. An exception would be Oncology protocols, which would be distributed to the Committee on a rotational basis. Primary reviewers would attempt to assess scientific merit, experimental design, and give some priority for funding. They would be provided the key references submitted by the principal investigator. Each primary reviewer would submit a written report to Clinical Investigation Service of his assessment of the protocol by the 15th of the month (see Incl #2). At his discretion, he could consult with the investigator, and/or another consultant reviewer and suggest modifications or simply submit a written report to Clinical Investigation Service.

The secondary reviewers would also be selected from the Committee, except that they would not have expertise or knowledge allied with the area under investigation. They would be selected on a rotational basis, would submit the same written reports as first reviewers, and would be especially expected to provide some degree of more remote perspective regarding the merit of a project.

E. The entire Committee would be provided copies of the protocol, primary review and secondary review. Attendance of the investigator at the meeting would be optional but he would be provided with a copy of the minutes which would contain the reasons for approval/disapproval. The written protocol would be expected to be sufficiently explanatory that only adjunctive information would be the only input requested of the investigator at the meeting. The entire Committee would consider the protocol and reviewer's comments and vote for approval/disapproval. The numerical estimation of scientific merit and priority for funding from the reviewers would be recorded in the minutes. The entire Committee would have an opportunity to revise the numerical estimate of scientific merit and priority for funding.

F. A list of volunteer consultants and their areas of expertise would be compiled from USUHS, AFIP, WRAIR and NNNMC.

II. Annual Review of Protocols

A. Henceforth, the Service will issue investigators lab notebooks, which will be available for inspection upon 24 hour notice and will be returned to Clinical Investigation Service upon completion of the project or the investigator's departure from WRAMC, at the discretion of the Chief, Clinical Investigation Service. For certain types of projects, a study record could suffice in lieu of a lab notebook.

B. Funded protocols which have been approved more than three years before must be resubmitted to the Committee for approval. Cooperative group protocols not requiring funding will be exempted from the three year limit. After three years, they are automatically considered terminated. Notice will be given to the principal investigator of these protocols three months prior to termination.

C. On a random basis, periodic inspections will be made of the data books, consent forms, and general status of individual work units. Written recommendations will be made to the Committee based on the basis of these inspections. At least one week notice will be afforded investigators. The Committee may elect to terminate a project or give the investigator time to correct deficiencies prior to a reinspection.

8 January 1979

WR 70-1

D. This year's Annual Progress Report will be divided into equal packages for each member of the Committee (see Incl #3) who can:

- 1) Certify that the Annual Progress Report is adequate and the project merits continuation.
- 2) Request additional data from the principal investigator.
- 3) Recommend the entire Committee closely scrutinize the project and decide whether or not continuation is warranted.

AUTHOR INDEX

Abraham, G: 8
 Alford, JP: 5,6,67
 Amedia, CA: 19
 Andersen, CA: 13,14
 Anderson, MC: 378
 Allen, SK: 317
 Altstatt, LB: 450
 Appleton, B: 286
 Annable, CR: 14,330,331
 Armstrong, JH: 9,10
 Armbrustmacher, VW: 15,16,50-1
 Arnold, TS: 444
 Arnstein, HRV: 454
 Atkinson, RL: 8

 Babcock, W: 238,336
 Baer, H: 378,395
 Bainbridge, SL: 14
 Ballows, M: 341
 Barr, CF: 11,282,284
 Baseman, R: 484
 Bass, JW: 15, 433
 Baylin, SB: 7
 Baxter, JD: 5
 Beattie, RJ: 130
 Bedynek, JL: 25,417
 Belville, WD: 336
 Bender, DR: 315
 Berenberg, JL: 261,451,456,458
 Bergdvin, PR: 217
 Bergman, SM: 19,23
 Berne, K: 8,9,10,342,349,365
 Bertovich, IJ: 474
 Blanco, C: 15
 Blessing, JA: 8,15
 Bleyer, A: 6,98
 Bluemle, ML: 475
 Boehm, TM: 7,36,42,49,50,56,62,89
 Boice, JA: 356
 Bongiovanni, B: 14,394
 Bongiovanni, R: 397
 Boone, CW: 454
 Borski, A: 221
 Brandt, W: 460
 Bray, GA: 8
 Bridenbaugh, RH: 54A,62A,438, 40,441,442,443
 Brill, JM: 8
 Brinton, C: 9,10,273

Brody, PG: 474
Brott, WH: 332
Broughton, RE: 7
Brown, A: 399
Brown, ND: 335
Bruton, J: 5,6,8,49,57,58,72,87
Burgess, DT: 432
Burke, JC: 450
Burkhalter, EL: 125
Burman, KD: 5,6,7,8,25,3035,36,38,43,45,46,47,48,54,54A,47,48,54,54A,
57,59,61,62,62A,63,67,70,74,76,77,78,94,96,97,99,100,102,
103,107,109
Butkus, DE: 22,23
Butler, W: 456
Bybee, DE: 6

Canfield, CJ: 276
Carbone, PP: 8
Cassimatis, E: 441
Castell, DO: 116,121,130
Casterline, CL: 353
Chaney, BF: 425
Charles, A: 6
Chism, S: 221
Chopra, I: 7
Christopher, WO: 19
Chulay, JD: 276
Ciak, J: 9,10,273
Claggett, P: 282
Clements, JC: 336
Clifford, B: 484
Cohen, L: 6,98
Collins, GJ, Jr: 13,14,279,281,284
Comis, RL: 201
Cooker, HS: 303
Cooper, MR: 201
Corcoran, RJ: 8,416,417,418,420,421
Corrigan, DF: 7,39,40
Cox, DH: 223
Cross, AS: 11,270
Crumrine, MH: 15,433
Cupples, H: 14,296,297
Curtis, DJ: 120
Cutright, DF: 506,507

Dahms, WT: 8
Dalrymple, JM: 450
Darley, FL: 303
Daughaday, CC: 263,450,460
Davia, J: 6,52,53,111
Davis, RA: 265,266
Dawson, E: 5,58

Denton, MJ: 454
deShazo, RD: 363,373,399
Desjardins, R: 7,276
Dhir, SK: 25
Dimond, RC: 5,7,8,29,39,40,51,104,106
Dinterman, RE: 5
DiSaia, PJ: 15
Dixon, JP: 500
Djuh, Y-Y: 5,8
Doctor, BP: 335,336
Dubois, A: 116
Duff, WP: 336,407
Durant, JR: 454

Earll, JM: 7,31,33,34,40,41,45,51
Edwin, DH: 439
Epps, RE: 14
Esposito, E: 506
Evans, R: 14,350,352,353,354,355,375,376,377,378,380,381,386,387,392,
394,395,396,397,400

Faden, AI: 503
Fairbanks, G: 303
Falkson, G: 8
Farley, P: 249
Fenkins, KM: 474
Ferguson, E: 282
Fishbein, WN: 502
Fischer, GW: 431,432
Fisher, DA: 7,433
Fleming, AW: 332,333
Fowler, JE: 336
Frank, MM: 14,376
Frantz, AG: 6,33

Gangji, D: 6,98
Gann, DS: 7
Garvin, AJ: 454
Gemski, MJ: 336
Georges, LP: 6
Gibeily, GJ: 12
Gibbreath, M: 9,10,273
Gillin, MT: 8
Glass, AR: 5,7,8,57,58,64,68,69,71,79,80,81,82,83,84,91,92,93,119
Glaubiger, D: 6,98
Clinos, AG: 8
Godat, RF: 448
Goodloe, S: 25
Green, DC: 13,333
Griffin, JL: 15,16
Gross, R: 11
Guilbert, TV: 386
Guyda, H: 7,8

Haddock, JB: 403,405,434
 Hamilton, LJ: 454
 Harden, LB: 426
 Haut, MJ: 451,455,458,462,466
 Heim, WJ: 225,231,240,245
 Heit, H: 248
 Heller, PB: 413,414,415
 Hendricks, LD: 276
 Herberman, RB: 225
 Hirata, RM: 124
 Hobson, RW: 12,13,273
 Hodges, W: 9,273
 Hofeldt, F: 6
 Hooper, RG: 264
 Horton, J: 104
 Howards, SS: 8
 Hreshchyshyn, NM: 15
 Hsu, SH: 7
 Hunt, KK: 389
 Hunter, JG: 440
 Huott, AD: 436,437,503
 Huss, RW: 377
 Hutchison, GB: 422,423,424

 Jampol, L: 289
 Jeffress, LA: 303
 Johns, M: 374
 Johnson, FB: 27
 Johnson, JP: 21
 Johnson, LF: 11,17,114,115,116,117,118,120,121,124,125,127,128,130,
 248,421
 Johnson, MC: 8,15,416,418,419,420
 Johnson, W: 303

 Kale, MP: 16
 Kaliner, M: 14
 Kaminski, RJ: 11,37,43,111,116
 Kark, JA: 16,451
 Katz, NNK: 298,417,455,462,463,464,465
 Keene, A: 484
 Kelser, P: 5
 Keren, DF: 474
 Keys, H: 149
 Kidd, GS: 5,57,58,65,74,85,86,90
 Kimball, DS: 11,237,251,399
 Klapholz, H: 402,403,405
 Klein, TA: 412
 Kleinberg, DL: 6,33
 Koduer, IJ: 474
 Koetitz, S: 335
 Kozloff, L: 13
 Kramer, KK: 286,288,298

Lader, J: 6
 Landes, D: 432,434,435
 Latham, KR: 5,6,8,94,113
 Laurence, PJ: 25,27
 Law, IP: 223
 Lawless, OJ: 342,349,356,389
 Lawley, TJ: 14,376
 Leaper, V: 426,464
 Lee, R: 408,409,410,411,413,414,415
 Lessin, LS: 16,463,465
 Levinson, AI: 14,352,363,364,374,375,376,394
 Lieblich, J: 7,8
 Light, JA: 327,328,330
 Lohr, F: 303
 Love, LR: 303
 Lowell, GH: 433
 Lowenthal, D: 28
 Luberoff, DE: 454
 Lukmire, NK: 317,320

 MacDermott, RP: 474
 Maddox, WA: 454
 Mahon, DE: 336
 Marcks, C: 374
 Marinelli, PC: 7
 Martin, B: 6
 McAllister, H: 25
 McCasland, JP: 506
 McClain, JB: 267
 McDonald, W: 239
 McLeod, DG: 335,339,340
 Mease, AD: 15,244,427,431,432,433
 Mehlman, I: 109
 Mellitt, R: 5,7,9
 Mendoza, E: 503
 Mesrobian, R: 426
 Metcalfe, DD: 381
 Miller, RG: 454
 Minifie, FD: 303
 Miskoff, AR: 219,222,228,231
 Mittemyer, BT: 223,239
 Montgomery, AA: 12,300,306,310,311,312,313,318,320,321,323,324
 Moore, J: 19,21
 Morgan, DW: 441
 Mosijczuk, A: 431,432
 Muir, RW: 124,228,249,451
 Mullunchick, E: 364
 Munster, AM: 454
 Murphy, PW: 506
 Muth, EB: 299

Nash, DA: 19,20,21,22,23,24
Nash, GS: 474
Neches, N: 403
Neglia, W: 400,401,415,422,424
Nickson, JJ: 423
Noel, GL: 31
Nsouli, KA: 19

Oakes, DD: 14
O Brian, JT: 6
Oldham, RK: 225
Olmert, JP: 241,243
Olson, JP: 241,243
Pamplin, CL: 276
Papineau, MB: 443
Park, RC: 8,15,125,130,262,400,401,408,409,411,413,415
Parmley, RT: 454
Parver, L: 14,297
Paulen, A: 484
Perlin, E: 8
Peura, DA: 17,124
Phillips, RA: 454
Pierson, D: 14,394
Pitts, A: 454
Poling, CR: 442
Pomerance, GN: 295
Poplack, D: 6,98
Prall, RH: 466
Pretlow, TG:
Prichard, J: 466
Prins, D: 303
Privitera, CR: 441
Prosek, RA: 12,300,306,310,313,318,320,321,324

Rabinowitz, M: 25
Radcliffe, JH: 333
Raife, MJ: 336
Rajfer, S: 6,52,53,111
Ramirez, DA: 387,396
Reardan, J: 7,8
Reid, RH: 123,471,474
Reingold, D: 14,387
Rice, JS: 119,124
Rich, NM: 12,13,14,279,282,284
Ricotta, JJ: 13,381
Rimm, W: 289
Roberts, D: 426
Roger, L: 401
Rogers, JE: 7
Rose, E: 6
Rosen, SW: 7,8
Ruymann, FB: 15,133,142,147,169,173,175,177,180,244,427,431,432,433

Sack, RL: 442
Sadoff, J: 267
St James, DN: 333
Salvado, A: 456,466
Sander, EK: 303
Sapolis, RJ: 443
Schaaf, M: 6,7,29,31,33,40,41,45,52,53,72,104,106,111
Scherr, CK: 12,299
Schlhamer, JH: 14
Schuchman, GI: 12
Schuster, DL: 14,355,392,394
Schwartz, DM: 12,300,306,308,310,313,318,320,321,324
Scialla, SJ: 11,228,249,282,284,451,458
Sedge, RK: 12,320,323
Sepulveda, R: 104
Setterstrom, JA: 15
Shay, SS: 128
Shelhamer, JH: 381
Sherman, CR: 303
Shingleton, HM: 15
Shou, HL: 8
Siedlecki, M: 19
Siegel, SR: 119
Silverberg, SG: 15
Simon, R: 8
Sjogren, RW: 474
Skiba, H: 402
Slayton, RE: 15
Smallridge, RC: 5,6,7,51,52,53,59,67,106,111,113
Smith, CE: 7,37,43
Smith, D: 5,7
Smith, LJ: 14,354,380,381
Snyder, K: 8,9,10,349
Speckart, SF: 11
Spees, EK: 14,326,329,505
Spencer, FC: 13
Spicer, SS: 454
Spriestersbach, DC: 303
Stein, MR: 128
Strum, D: 7
Stutzman RE: 334,336
Sullivan, EF: 475
Summers, RJ: 14,375,376,377,380,386
Surr, RK: 12,308,317
Swan, KG: 12
Swerdloff, RS: 5,7,8
Sweet, RB: 336

Tarassoff, G: 16,463,464
Taub, M: 6
Taylor, G: 458
Tellis, CJ: 11
Terrell, R: 9,10,349
Thompson, P: 7,37
Thrall, JH: 8
Tischler, A: 113
Tormey, DC: 8
Tramont, EC: 9,10,11,269,271,273,274,276,278
Tucker, RR: 389
Turkeltaub, PC: 395
Van Swol, RL: 446,448
Vigersky, RA: 5,6,7,8,55,57,58,65,75,87,88,90,98,108,110
Vura, RC: 425

Walden, BE: 12,300,306,310,313,318,320,321,324
Walker, PF: 397
Walldorf, MA: 11
Wamble, JL: 440
Wannemacher, RW: 5
Ward, GW, Jr: 351
Wartofsky, L: 5,6,7,8,28,29,31,36,37,39,40,51,57,59,67,74
Washburn, TB: 8
Webster, HK: 466
Wehrle, PA: 383
Weidig, JC: 19
Weinberger, PC: 454
Weinrieb, GS: 474
Weir, EE: 454
Weltz, MD: 124
Wergeland, FL: 298
Whelton, JC: 349
Whitcomb, ME: 341
Whitmore, PV: 14,295,296
Wilbur, RD: 351
Williams, ER: 444
Wilson, JKV: 454
Wong, RKH: 117,120,121,127,339
Woods, M: 16,464
Wray, HL: 5,6,8,59,66,67,72,74,85,86,104,106
Wright, CB: 12
Wright, S: 285
Wyler, DJ: 278

Zarda, PR: 25
Zaremba, JL: 454
Zettergren, JF: 454
Zimmerman, DH: 9,10,349

Work Unit No.: 1647

Title of Project: Inhibition of Red Cell Pyridoxal Kinase by the Carbonyl Reagents, Isoniazid and Hydralazine

Investigators:

Principal: LTC John A. Kark, MC

Associate: LTC Michael J. Haut, MC

Objectives: To elucidate the mechanism of the anti-B₆ side effects of these drugs and to define the time-course of these effects.

Technical Approach: Methods have been described in detail in previous protocols and interim reports. This year we have synthesized the putative inhibitor of pyridoxal kinase, the pyridoxal hydrazone derivative. We have shown that inhibition of red cell pyridoxal kinase occurs at the expected low concentration (10^{-6} M in pyridoxal-isonicotinyl hydrazone, PL-INH). We are in the process of devising an assay for this compound in red cells.

Progress and Results: Pyridoxal-isoniazid hydrazone (PL-INH) could be detected by fluorescence in hemolysates, but the amount of fluorescence varied as the log of concentration. On-going work concerns obtaining conditions for lineal assay of PL-INH concentration.

Conclusions: PL-INH can be detected in hemolysates. Further work is needed to obtain a quantitative measurement of red cell levels.

Funding Requirements: None

Publications: None this fiscal year

Type of Report: Interim

Work Unit No.: 6009

Title of Project: Clinical and Laboratory Investigation of
Meningeal Leukemia

Investigators:

Principal: Frederick B. Ruymann, M.D., COL, MC

Associates: Alan Mease, M.D., MAJ, MC
Askold Mosijczuk, M.D., MAJ, MC

Objectives: Comparison of biochemical and immunological variables in the cerebrospinal fluid of patients with Acute Lymphocytic Leukemia under treatment with intrathecal methotrexate vs. intrathecal methotrexate and CNS irradiation.

Technical Approach: Patients with leukemia under the direct and consultative care of the Pediatric Hematology/Oncology Section will be used as the primary source. Additional patients will be studied. Clinical histories, flow sheets, and summaries are already maintained by child and adult oncologists at present. Particular note will be made of the time of diagnosis, length of remission, past history of CNSL, and therapy for CNSL and type of prophylactic CNSL treatment. As new patients are acquired on #7411 they will be followed along. Spinal fluid and blood specimens will be obtained. Patients in clinical remission will have confirmatory bone marrow aspirated and spinal fluid analysis every two months. This consent will be obtained on all procedures. This protocol involves no procedures beyond those already recommended for ALGB.

Progress and Results: The main laboratory, WRAMC has cyto-centrifuge capability with competent interpretation of results available on a routine basis. We have monitored this capability over the past 2-3 years.

Conclusion:

- (1) Discontinue funding of this project #6009.
- (2) These studies now exist as routine procedures in the Department of Pathology.
- (3) Continue to keep the cytocentrifuge in the Laboratory of Developmental Diagnosis under the direction of Dr. Mease, since this centrifuge is used regularly in ongoing work with white cell function.

Type of Report: Terminated

DISPOSITION FORM

For use of this form, see AR 340-13, the proponent agency is TAGCEN.

REFERENCE OR OFFICE SYMBOL

HSWP-OCR

SUBJECT

Request for An Annual Progress Report, FY-78.

TO Richard Gardner, MD
Dept of Peds

FROM C, Clin Inv Svc

DATE 12 Apr 79

CMT 1

1. Despite multiple written and telephonic requests from this Service, no FY-78 Annual Progress Report (APR) has been received for Work Unit #6013, Evaluation of Four Modes of Therapy of Reyes Syndrome, Acute Encephalopathy with Fatty Infiltration of the Viscera: A Multi-Hospital Study.

2. Unless an APR is received by 20 April 1979, the Clinical Investigation Committee has voted to:

- 1) accept no future protocols from you
- 2) terminate funding for any other of your protocols


TIMOTHY M. BOEHM

MAJ, MC

Chief, Clinical Investigation Service

HSWP-K

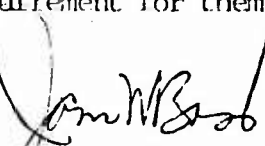
TO C, Clin Inv Svc

FROM C, Dept of Peds

DATE 17 Apr 79

CMT 2

Doctor Gardner was reassigned to Germany upon completion of his training at WRAMC Jun 78. As physicians frequently seem to PCS without submitting final annual progress reports it is suggested that it be a requirement for them to outprocess through your Service.


JAMES W. BASS, M.D.

Colonel, MC

Chief, Department of Pediatrics

Work Unit No.: 6014

Title of Project: Granulocyte Transfusion in Children: A comparison of continuous flow centrifugation and filtration leukophoresis

Investigators:

Principal: Frederick B. Ruymann, M.D., COL, MC

Associates: Alan Mease, M.D., MAJ, MC
Askold Mosijczuk, M.D., MAJ, MC
Mark Simpson, M.D., MAJ, MC

Objectives: The goal of this research is to compare two methods of granulocyte collection and subsequent transfusion in children. Comparisons of effects on donor and recipient and planned with specific investigations of granulocyte chemotaxis and other basic function studies.

Technical Approach: The basic method for granulocyte collection by continuous centrifugation and outlined in the attached publication. The method for filtration leukophoresis is outlined by the protocol and follows standard published methods. The experimental design involves sequential daily transfusions to an eligible patient using alternating collection methods from the same donor. Comparisons will then be made of donor reaction, recipient reaction, and granulocyte parameters as outlined by the protocol.

Progress & Results: A recent addendum to this protocol has been issued, see attached. White cells for granulocyte transfusion therapy are principally obtained from the Blood Donor Center, American Red Cross. The arrival of the white cells occurs very late in the day, generally after 1700 hrs. This late arrival time precludes extensive in vitro testing as planned by this protocol. In vivo data, such as 1 hour recovery data will continue to be obtained, however.

The informed consent must continued to be used to comply with FDA regulations, since white cell transfusions are considered investigational.

Conclusions:

- (1) Continue this protocol #6014 for another year.
- (2) MAJ Terry Pick, Fellow in Pediatric Hematology/Oncology will perform a review of recent granulocyte transfusions in children, WRAMC and prepare a publication.
- (3) In-vivo data and informed consent procedures will be followed.

(4) A new granulocyte transfusion protocol is planned for next year.

Funding Requirements: FY 79:

Travel: Training - \$500 Travel to present results of this project at a national meeting.

Type of Report: Interim

Work Unit No.: 9037

Title of Project: Women's Knowledge of Breast Cancer and
Breast Self-Examination

Investigators:

Principal: 2Lt. Shelly K. Rogers, ANC, Staff Nurse,
Ward 67, WRAMC.

Associate: Maj. Susan B. Shipley, ANC, Nursing Research
Service, Dept. of Nursing, WRAMC.

Objectives: The purpose of this study was to (1) determine women's level of knowledge of breast cancer and breast self-examination; (2) to ascertain any significant correlation between demographic information and/or knowledge and actual practice of breast self-examination; and (3) to gather base line data in preparation for the development of an educational program for women about breast self-examination.

Technical Approach: The above stated objectives were achieved in a comparative survey study method. 532 adult women over the age of 20 visiting the OB-GYN clinic were interviewed, provided an explanation of the study, and asked to sign a consent form by one or both investigators. Each woman was then asked to complete a 15-question instrument consisting of 6 questions related to demographic data and 9 questions related specifically to breast cancer and breast self-examination. Correct answers for at least 80 percent, or 7 out of the 9 questions related to knowledge represented the acceptable standard or a passing score.

Progress and Results: After tabulating the answers from each of the 532 questionnaires, it was found that 60 percent of the women achieved the acceptable standard, and were found knowledgeable of breast cancer and breast self-examination. On the other hand, 40 percent of the women did not achieve a passing score and lacked knowledge of both breast cancer and breast self-examination. Of the total sample, only 53 percent of the women actually practiced monthly breast self-examination. 45 percent of the women were 20 to 29 years of age. The education level of the sample was significantly high. 98 percent had at least a high school education, with 53 percent of the total sample having graduated from college.

Conclusions: Despite the increase in publicity and information available to women on breast cancer and breast self-examination over the past several years, a significant number of women still lack vital information essential to the performance of breast self-examination. The obvious implication here is the necessity of health teaching.

Women can only practice acceptable breast self-examination if they possess an adequate knowledge base.

Funding Requirements: None

Publications: There are no publications to date. Manuscripts for future publications will be forwarded to the Clinical Investigation Service at such times.

Type of Report: Final

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